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CONTENTS

The Frank E. Bunts Institute 13

Trigeminal Neuralgia.
W. James Gardner, M. D., Department of Neurosurgery 165

Management of the Patient with Nervous Exhaustion.
Charles L. Hartsock, M. D., Department of Medicine 173

A Case Illustrating the Analogy Between Essential Hypertension and Raynaud's and Buerger's Disease.
George Crile, M. D., Department of Surgery 184

Some Endocrine and Related Factors Influencing Spermatogenesis.
William E. Lower, M. D., Department of Genito-Urinary Surgery, Eugene Cutuly, Ph.D., and D. Roy McCullagh, Ph.D., Department of Biochemical Research 187

Neuralgia of Dental Origin.
C. A. Resch, D.D.S., Department of Dentistry 199

The Surgical Treatment of Diverticulitis.
Thomas E. Jones, M. D., Department of Surgery 207

Effects of Light, Sun, and Other Rays on Growth.
Otto Glasser, Ph.D., Department of Biophysics 212

Management of Chronic Peptic Ulcer.
John Tucker, M. D., Department of Medicine 220

Successful Use of Prontosil in a Severe Case of Streptococcus Septicemia Following Cystoscopy and Peri-Urethral Abscess.
Charles C. Higgins, M. D., Department of Genito-Urinary Surgery and F. C. Schlumberger, M. D., Fellow in Surgery 232

THE FRANK E. BUNTS INSTITUTE

announces

A Course In

Diseases of the Skeletal and Nervous Systems

on

MONDAY, TUESDAY, and WEDNESDAY
NOVEMBER 8, 9, and 10, 1937

A description of the course and an outline of the subjects to be covered will be found on page 237.

TRIGEMINAL NEURALGIA

W. JAMES GARDNER, M. D.

Trigeminal neuralgia or tic douloureux is a lancinating, paroxysmal pain in the distribution of one or more of the branches of the trigeminal nerve. Each paroxysm lasts only a few seconds and is frequently likened to an electric shock. It is a disease of middle and later life but occasionally appears in young subjects. In the beginning, the pain is confined to one branch of the nerve, most frequently the infra-orbital, but with the passage of time it tends to spread to the other branches. The mandibular branch is somewhat less often the site of origin and the supra-orbital branch is very seldom involved primarily. The disease affects both sexes about equally and in approximately 2 per cent of the cases the pain is bilateral.

The cause of trigeminal neuralgia is not known. By the patient, however, the teeth are always looked upon with suspicion because of the location of the pain and because it resembles that produced when a dentist's drill touches a sensitive pulp. Furthermore, the pain is frequently incited by touching a tooth or by chewing. Despite this, however, it can be said with authority that no dental condition, however neglected and aggravated, can cause tic douloureux. Within a few months of the onset, these sufferers have several or perhaps all of their teeth removed, usually at their own insistence and always to no avail. In the first complete description of this disease in 1804, Samuel Fothergill[1] suspected that "the cause of these extreme pains in the face might possibly be of a cancerous nature." This idea, of course, has long since been proved erroneous. Frazier[2] has recently advanced a theory that trigeminal neuralgia is caused by a lesion, probably of vascular origin, in the external thalamic nuclei and he has offered considerable evidence in favor of this view. Time and the opportunity to examine a sufficient amount of autopsy material will determine the correctness of this theory. In an occasional case, the pain of tic douloureux is due to pressure on the root of the nerve by a tumor or aneurysm.

The intervals between paroxysms are usually entirely pain-free but the patient lives in constant dread of the next attack. He learns that certain actions—such as talking, eating, drinking, blowing the nose, shaving, and washing the face—are especially likely to bring on a paroxysm. When certain small areas, called trigger zones, are touched, a paroxysm is apt to be incited. These trigger zones may be anywhere within the area of the trigeminal nerve but are especially frequent on the upper lip, the ala of the nose, and the upper alveolus. A light touch in these areas is more apt to induce an attack than is heavy pressure. At times there are latent intervals during which no form of stimulus will

incite an attack. A latent interval frequently occurs while the patient is in the doctor's office so that the patient is led to remark, "Why, it is just like going to the dentist, my pain is gone!"

Spontaneous remissions are a characteristic of trigeminal neuralgia. They occur more frequently and last for a longer time in the early stages of the disease. In exceptional cases the pain may be absent for as long as three years. With the passage of years the pain seems to become more fixed, more extensive, and the remissions are shorter and fewer. As in the case of multiple sclerosis, these spontaneous remissions may lead to misconceptions regarding the efficacy of various attempts at treatment. Not infrequently the patient will report that the removal of a tooth, a change in climate, or the use of some new medicine "cured the pain for six months" when, as a matter of fact, the "cure" was a spontaneous remission. Occasionally, trigeminal neuralgia appears as a symptom of multiple sclerosis and, in England, a familial form of the disease occurs in association with multiple sclerosis[3].

In making a diagnosis of trigeminal neuralgia, the doctor is dependent entirely on the patient's description of the pain because primary objective findings of this disease are entirely absent. Usually, however, there are secondary outward signs which should be sought out. In many cases a voluntary "splinting" of the facial muscles is caused by the patient's endeavor to ward off attacks. For this reason, the facies may be mask-like and the patient will talk and sometimes drool out of the opposite corner of the mouth. Because talking is so apt to incite a paroxysm, these patients usually bring a relative to the doctor's office to do their talking for them. Touching the face is also apt to incite a paroxysm, and, for this reason, the painful side of the face may not be washed as thoroughly as the opposite side, in which case the skin is more oily, especially about the ala of the nose. During severe attacks, cleansing of the mouth is avoided, debris accumulates on the teeth, the tongue is coated, and the breath foul. The reaction to the paroxysm differs with the patient but usually follows a set pattern in each case. One patient may suddenly become immobile, "freeze" so to speak, with the onset of each pain; another may grimace; another may grab or rub the face firmly; and the more neurotic patients have been known to actually roll on the floor. Flushing of the face and lacrimation are occasionally present during paroxysms. In testing the sensation in patients with tic one finds as a rule a definite over-response to painful stimuli. These patients are apt to withdraw very quickly from a slight pin-prick even though it is not the painful area which is being tested.

There is undoubtedly a "tic constitution." Frazier[2] has stated that patients so afflicted are more or less temperamentally alike, admitting exceptions, no matter what their station in life or their occupation. He

finds that these patients have always been apprehensive and disposed to worry about minor matters, but no matter how long the duration or how intense the pain, they do not become addicted to morphine. It seems to me that the condition is more common in the rural than in the urban population. There is a definite tendency for these patients to seek out fellow sufferers, so that the average patient knows of as many cases as the average physician will encounter in a lifetime of practice. I agree with Frazier that hypertension, arteriosclerosis, impaired renal function, and arthritis are encountered in this group of patients more frequently than in those of a corresponding age group who are unaffected. Despite this, longevity seems to be the rule. These patients do not like to go to bed because of pain, so they usually are up and around even when seriously debilitated by very frequent paroxysms and the attendant starvation.

Another disorder which frequently is confused with trigeminal neuralgia is referred to as "atypical neuralgia." This pain differs from trigeminal neuralgia in that it is constant and not paroxysmal, it is pressing and burning in character rather than sharp and lancinating. It usually extends well beyond the distribution of the fifth nerve into the occipital region, behind the ear, and down the side of the neck. The patients are very neurotic and while informing the doctor of the severe agony which they are suffering they exhibit no outward sign of pain. They are content to lie in bed and be waited upon. The pain usually originates following some manipulation, especially extraction of teeth. All efforts to relieve the pain by alcohol injections, nerve resections, or by operations upon the sinuses or teeth merely tend to aggravate the pain. I do not know what the end result is in these cases but I have never seen a patient permanently cured. These patients frequently are afraid they have tic douloureux when, as a matter of fact, they would be far better off if they did have it, at least insofar as relief of pain is concerned. These patients welcome operative procedures but are always made worse by them. Patients with true tic, on the other hand, avoid operation as long as possible but are pleased with the result.

Treatment

What is to be done for the patient with trigeminal neuralgia? In answer to this question, one may say that only two forms of treatment are worthy of the name—alcohol injection of the peripheral branches of the fifth nerve and resection of the sensory root of the nerve within the cranial cavity. Inhalations of a volatile preparation called trichlorethylene may diminish the pain in 10 per cent of the cases, but it very seldom gives satisfactory relief. Other forms of medical treatment are of no avail. Operations upon the teeth and sinuses are to be deplored.

Peripheral resections of the infra-orbital and mandibular nerves do not give as long a period of relief as do subzygomatic alcohol injections. Resection of the supra-orbital nerve may be used instead of alcohol injection of this branch but the period of relief is short. This supra-orbital branch is so rarely involved primarily that its treatment is seldom indicated. Destruction of the gasserian ganglion by the injection of alcohol or by electrocoagulation by the closed method entails unjustifiable risks when one considers the safety of the generally accepted methods.

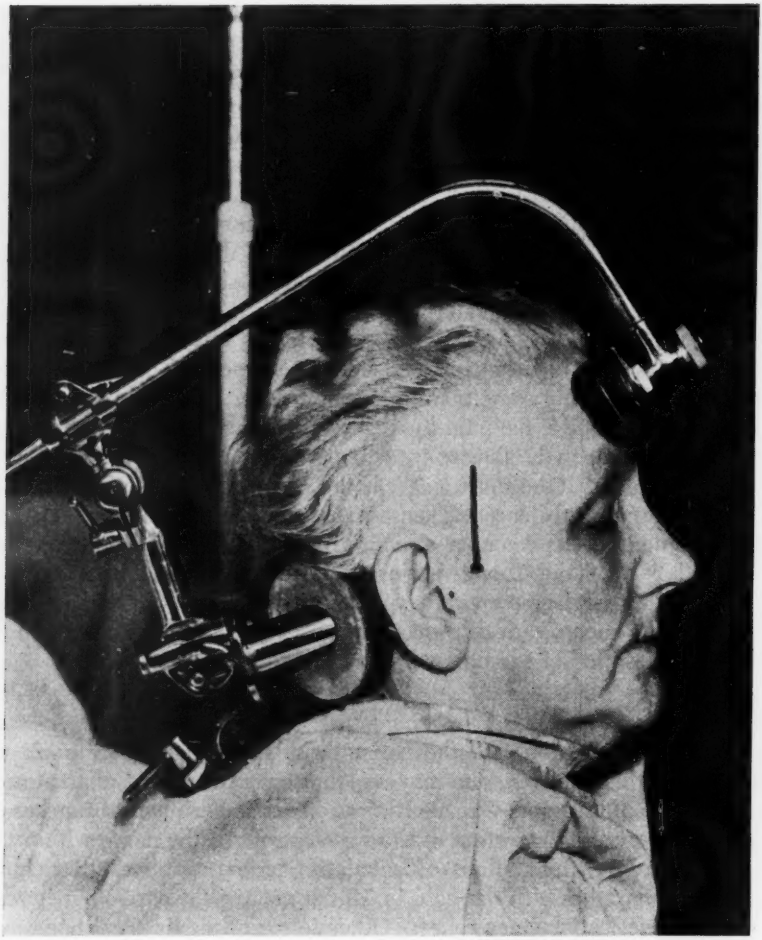

FIGURE 1: The patient is in position for operation and the skin incision is indicated.

A good practice when confronted with a case of trigeminal neuralgia is to ask the patient if he would prefer numbness of the face to the pain. If the patient has genuine trigeminal neuralgia, he will not hesitate but will at once choose numbness. He may then be told of the two preferable methods of producing this numbness and be allowed to choose between them. As a rule the patient will choose alcohol injection if he has not had the pain very long, but if he has had previous alcohol injections, he usually wants the operation which will give him permanent relief. Of course, if there is any question about whether the patient has genuine

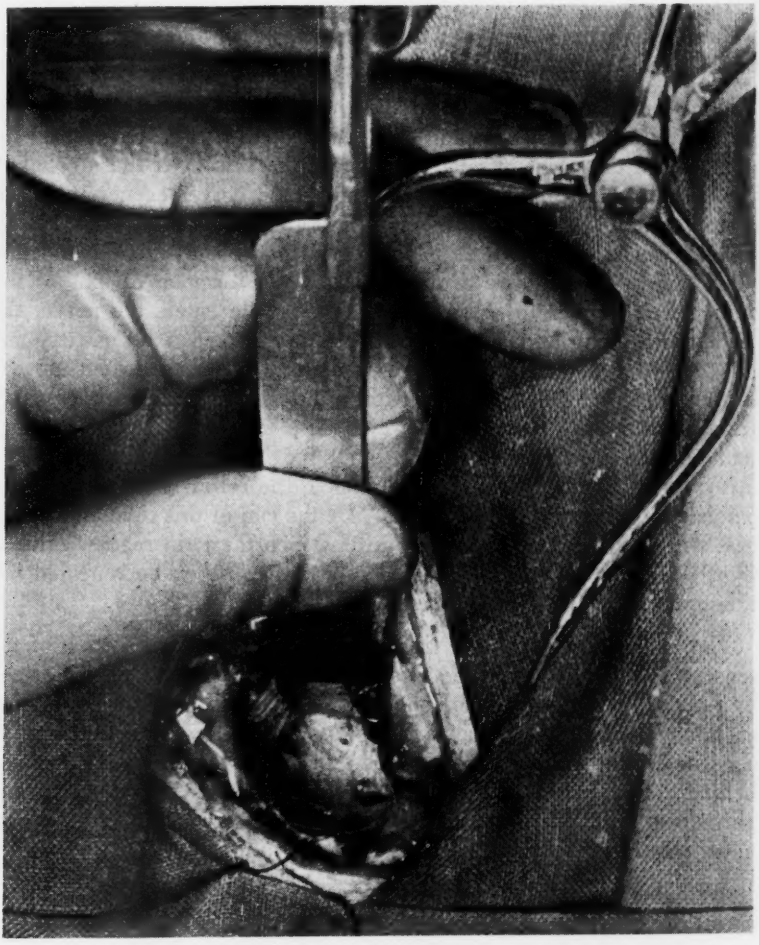

FIGURE 2: The sensory root fibers can be seen through the opening in the sheath.

trigeminal neuralgia, the operation is never advised. In such cases the alcohol injection is a diagnostic as well as a therapeutic agent. If the patient has genuine trigeminal neuralgia and the painful area is made numb by the injection of novocain and alcohol into the nerve, the pain is immediately stopped and no stimulus will bring it on. If the neuralgia is of the atypical form, the injection will not relieve it at once or, if it does so, the pain will recur long before the resulting anesthesia wears off. An alcohol injection can be done far more accurately with local than with general anesthesia. The pain produced by the injection is comparable to a paroxysm. The disadvantage of the injection method of treatment is that when the operation is finally decided upon, the patient has suffered in the meantime and is from one to several years older and therefore may not be quite as fit for operation.

If the treatment is to be alcohol injection, the subzygomatic route is the one of choice. By this method the second or third division can be interrupted at the point of emergence from the skull. If the alcohol is introduced at some more peripheral point, the nerve regenerates more rapidly and the period of relief is correspondingly shorter. In a subzygomatic injection, the needle is introduced in front of the ear and just below the zygoma and is directed toward the foramen of exit of the branch it is desired to inject. When the needle enters the nerve, the patient will experience a sharp pain similar to one of his paroxysms. One cc. of 2 per cent solution of novocain is then injected slowly. If the point of the needle is within the nerve, the numbness will appear within two minutes, in which case 0.6 to 1.0 cc. of 95 per cent alcohol is injected slowly without moving the needle. If satisfactory anesthesia of the skin is obtained, the relief is immediate and persists for nine to eighteen months. By the end of this time, the numbness will usually have cleared up after which the pain recurs within a short period of time. The alcohol injection can then be repeated but subsequent injections become slightly more difficult.

The modern operation for trigeminal neuralgia is a resection of the sensory root. This operation was suggested by Spiller and performed by Frazier in 1901[4], and soon superseded the Hartley-Krause operation of removal of the gasserian ganglion. The Spiller-Frazier operation consists of the division of the sensory root fibers of the fifth nerve just behind the ganglion. It results in permanent numbness of the face and permanent relief of pain because these preganglionic fibers, once divided, never regenerate. The present technic is as follows:

With the patient in the sitting position and under light ether narcosis, a vertical incision five centimeters in length is made just in front of the ear and down to the zygoma (Fig. 1). The scalp and temporal muscle

are retracted and an opening the size of a fifty cent piece is made in the squamous portion of the temporal bone. The dura is then elevated from the floor of the middle fossa of the skull, following the course of the middle meningeal artery to its point of entrance through the foramen spinosum. A bit of cotton on a dental applicator is forced into this foramen in order to occlude the middle meningeal artery which is then severed. Just anterior and mesial to the foramen spinosum the gasserian ganglion is encountered at the point where its third division leaves the skull through the foramen ovale. The dura is stripped upward from the lateral surface of the sheath of the ganglion and sensory root. As the sheath is opened posterior to the ganglion, the sensory fibers can readily be picked up on a nerve hook and divided (Fig. 2). If the patient has had no pain in the forehead, one or two small fasciculi to the first division are spared. When this is done a postoperative keratitis never occurs. This procedure of sparing the ophthalmic fibers was devised by Frazier and it marks a definite advance in the treatment of trigeminal neuralgia. If the entire sensory root is divided, a keratitis will develop in an occasional patient but this clears up promptly when the cornea is properly protected. The motor root of the fifth nerve which supplies the muscles of mastication can readily be identified and spared. It is especially necessary to spare this motor root in bilateral operations; otherwise the patient would never be able to chew. Dividing the motor root on one side causes no disability except some facial asymmetry due to atrophy of the masseter muscle.

After an operation of this sort, the course is surprisingly smooth and the patient is discharged on the seventh day. A very small amount of ether is necessary for anesthesia in these cases, presumably because of the erect posture, and there are no complications from the anesthetic. The only mortality in the author's series occurred in an elderly man who insisted on avertin anesthesia. His sudden death during the operation was ascribed to coronary disease, however, and not to the anesthetic. The risks of the operation are so slight that it is very seldom that a patient is considered unfit for it.

Hundreds of cases are on record with a mortality of less than 1 per cent, these operations having been performed by various surgeons. In view of the slight risk of the operation and the permanency of the cure, some surgeons have refused to give alcohol injections and have insisted that their patients have the operation. This is perhaps a good course to pursue, for once the natural timidity of these patients is overcome and their pain is relieved by operation, they are eternally grateful.

In the entire realm of surgery there is probably no more satisfactory operation than Frazier's subtotal resection of the sensory root of the fifth nerve. The gratitude of patients relieved by this procedure is in

some cases really pathetic. In the well-balanced individual there are no unfavorable sequellae. The very neurotic patient may complain of the numbness or of a sensation of tickling, itching, or burning in the numb area. Occasionally there are "ghost pains" which last for some time after operation. These "ghost pains" are sudden darting sensations just like the former paroxysms except that they are painless. When the patient is convinced that they do not indicate a return of the former pain, they are disregarded.

Another method of approach has been described by Dandy[5] who advocates division of the sensory root of the fifth nerve at the pons. This method, however, will never be generally adopted. Neurological surgeons are almost universally agreed that this approach is more dangerous both to life and function than is the foregoing temporal approach, besides which it offers no practical advantages.

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MANAGEMENT OF THE PATIENT WITH NERVOUS EXHAUSTION

CHARLES L. HARTSOCK, M.D.

After a good American breakfast, topped off with a second cup of coffee, Mr. Brown rushed for his coat and hat and dashed for the garage on the first subzero morning of the winter. He had allowed himself the usual 20 minutes to get to his office where he would be busily occupied all day with perplexing business problems. This morning, however, only the slow growl of the starter mechanism greeted his push of the starter button. Mr. Brown then realized that for several weeks he had noticed the light had been dimming considerably when he started the car, but he hadn't paid any attention to this evidence of an exhausted battery. The result was that he was moderately inconvenienced this morning when the added strain of turning over a very cold motor was more than the already weakened battery could overcome. A short, but rather impatient, delay of an hour while the service man changed the battery and the slight expense of having the battery recharged were very trivial consequences, indeed, to pay for his negligence in observing that the additional electrical gadgets that he had recently installed were taking more energy out of the battery each day than the generator was restoring.

This experience with the battery meant very little to Mr. Brown, however, when six months later he began to feel fatigued, noticed some increasing irritability, a change in his disposition, and toward the end of the day a distinct need for a stimulant which he took in order to keep up his usual pace. At this time, he was engaged in an important piece of work that required more of his time and concentrated attention than usual. He soon became more irritable, was annoyed by the children, had trouble in getting to sleep, and was quite perturbed by his depressed spirits, his inability to concentrate and make decisions as was his custom. He was still in the midst of his important business and forced himself to carry on although his work was becoming quite inefficient. He was acutely aware of this and was haunted by the fear that his employers would discover it. It wasn't long until he began to have some digestive disturbances, and then he started to experiment with his diet and consequently lost some weight. It was only when he experienced some vague, peculiar feelings in his head and had had an occasional crying spell without the slightest provocation that he decided to consult his physician. He was certain there was some physical basis for his trouble because he had always been able to forge ahead and do more work than the average man and, although he realized that he had undergone some added strain during recent months, he had often done the same thing before. Still his experience with the battery on the cold morning meant nothing to him.

The physician whom he consults is immediately confronted with a difficult problem.

This clinical syndrome is of course not limited to business executives, but it may well be applied to Mrs. Jones who has several active children, an overworked school teacher, or to any one who is expending more nervous energy than can be restored during hours of rest and relaxation.

It is very easy for the physician to appreciate that there is some relation of such symptoms to the excessive consumption of nervous energy. It is not sufficient, however, just to advise the patient to take a vacation of several weeks or, as is sometimes prescribed, to take more physical exercise or to busy himself with other lines of activity in order to snap out of the "blues."

The difficult problem in these cases is the task of determining whether there is some vague, underlying organic pathology that has been slowly sapping the patient's vitality and acting as an extra load on his energy-producing mechanism. On the other hand, as in the case of the battery, the exhaustion may be due entirely to excessive drain of energy and an unbalanced energy-consumption, energy-production rate.

A double responsibility devolves on the physician in these cases. First he must institute a scrutinizing search for disease, not only because it is of the utmost importance to locate the hidden source of energy loss, but of prime importance to convince the patient of the absence of such disease if it does not exist. The emotion of fear becomes very dominant in the too nervous patient and most frequently takes the form of fear of disease. These fears are best controlled by the confidence that the examining physician may exert through his methods of examinations. Many examinations that seem unnecessary and a waste of time and money must be made to relieve the patient's fears. For example, a common fear that has arisen in the lay mind in recent years, owing to much publicity, is that of brain tumor. It seems that nearly every one with peculiar feelings in the head combined with some changes in personality has heard or read of somebody with brain tumor who had just the same symptoms. It is true that cerebral neoplasm must be very carefully considered in the differential diagnosis but, from the viewpoint of the patient, a roentgen examination of the head is one of the most satisfying examinations the physician can make although actually it is of little real value in the diagnosis of brain tumors.

The responsibility of locating or disproving the presence of disease is slight in comparison to the responsibility of deciding the rôle that any discovered abnormality may play in the patient's symptoms. Rare is the patient in whom at least some minor ailment cannot be found and the greatest discretion and judgment are necessary in evaluating the relation of this to the patient's trouble. This is necessary in order that

insult may not be heaped on injury by advising that some therapeutic regimen or procedure be followed that will only further exhaust the meager store of nervous energy. Many of the symptoms that point indefinitely to disease are a result, rather than a cause, of the exhausted state. Uncertain procedures must never be attempted in a hurry, and the timing of absolutely necessary therapeutic measures requires unusual understanding of the patient's possible reaction to such procedures.

That the energy-producing and energy-dispensing mechanism of all people is not the same requires no keen observation and is almost axiomatic. The fact remains that, in our struggle for existence, a certain amount of energy is required for merely maintaining existence. Considerably more is required to satisfy those inner feelings of self-respect, ambition, and other cravings of an emotional nature. It is in the latter or emotional make-up that the human race varies so greatly. Every individual possesses an emotional pattern just as different from that of other individuals as is the physiognomy of his face or the contour of his body. It appears unquestionable that inherited genes furnish the basic pattern that shapes the emotions, but the environment that gives the opportunity for the emotions to be displayed is the test of the real quality of the underlying structure. Differences in the outward appearance of the body are appreciated and readily accepted by all. Variations in the ability to acquire knowledge from teaching and experience are appreciated by most. Dissimilar structural design of the body is recognized by students of medicine as the cause of many of the diseases of mankind. A knowledge and understanding of the dissimilarity of the emotional tone of individuals and how this accounts for his behavior must also be fully understood by those physicians who would attempt to administer aid to the nervous patient.

The psychologists have studied the inherited differences of emotional tone and the manner in which it affects the responses to the objective stimuli of the environment. The character and personality of the individual are the results of the environmental force acting on the hereditary emotional pattern. It is not the purpose of this paper to enter into a discussion of the various classifications that psychologists have devised for the different personality groups. Those extremes of personality and emotional types that eventually terminate in the more serious psychoses are excluded also. I realize, of course, that it is only a matter of degree of emotional instability between the patient with extreme manic depression and the patient whom I am discussing as suffering from nervous exhaustion. I prefer, however, to limit my discussion to those individuals who do fall in the normal range of psychological behavior and would remain so if the fatigue caused by the stresses and strains

of life did not lower their reserve of nervous energy to the level where abnormal psychological behavior appears.

This group is seen more frequently by the internist and the family physician than by the psychologist. This is because the patient's symptoms are chiefly referred to the somatic domains of the body and only rarely do the emotional changes progress beyond what the patient believes by experience to be the normal manifestation of severe emotional upset. He is concerned with why these come on without any apparent cause and he may have definite fears for his sanity, but he still retains sufficient insight to try to explain his trouble on the basis of bodily disease.

In my experiences, patients who most frequently show the symptoms of nervous exhaustion can be conveniently grouped into three fairly distinct types of personalities.

The first, and by far the largest, group is comprised of young or middle-aged adults, usually females, who are above the average in mentality, frequently are attractive in physical appearance, and are inclined to possess some artistic talent. These persons are easily elated and just as easily depressed. They are extremely neat in their work and appearance and in their youth they appear to possess abundant energy and ambition so that they usually have many friends. They are restless, unable to relax easily, and worry excessively over trivial matters. They begin to notice fatigue after going through some of the usual stresses of life such as college experiences, childbirth, or illness. Following this, they never feel rested and gradually become more and more fatigued, eventually complaining of many indefinite symptoms in various parts of the body.

I choose to think of this group as the race horse type, unusually attractive and capable of speed, but attempting both to maintain the speed of the race horse and the stamina of the work horse. Insufficient rest to compensate for excessive use of energy is the downfall of these patients.

The second group has been seen more frequently in recent years. Highly capable, unusually ambitious, and endowed with a robust constitution, patients in this group are predominately masculine. Under ordinary conditions of life, they should be able to carry on until old age without any more ills than the usual acute infections. In the fourth or fifth decade of life, however, they begin to notice excessive fatigue, irritability, and the need for stimulants as cited previously. These are the men who, because of the necessity of the competitive struggle of making a place in the world, because of excessive ambition, or because of their unusual capabilities, are having additional work constantly thrust upon them. The result is a slowly ebbing reserve of nervous

energy until the level has reached such a state of exhaustion that normal functions are interfered with. I choose to think of these individuals as marathon runners whose goal should be life span, but because they set their pace too rapidly they must fall by the wayside and watch the slower but better paced runner reach the goal.

The third group is smaller, but the patients have a very distinct personality and it is much more difficult to explain the mechanism causing the loss of energy. Patients in this group are about evenly divided as to sex. The onset of exhaustion is late in the fifth or sixth decades. They are unusually good, quiet, peaceful citizens and unusually conservative in their work and dealings with their fellow men. They are of the slow, plodding type, extremely cautious, and not inclined to take on more responsibilities than they can handle well. They are not inclined to be overly social with their fellow men, preferring to be lone wolves. All their lives, however, they have paid undue attention to details and their lives are built around the clock. When the break comes the result is predominately one of melancholia and depression. It is probably due more to a psychopathic personality than to undue consumption of energy. These patients have scrupulously devoted themselves to ceaseless hard work for a cause and show many of the signs of degenerative diseases which probably affect the energy-producing, energy-storing mechanism. This is more frequently the cause rather than exhaustion due to excessive consumption of nervous energy. I choose to think of this group as confining their ceaseless, plodding activity in a too narrow groove with an actual wearing-out process which accounts for a more permanent type of trouble than a mere exhaustion of an otherwise normal mechanism.

After this general introduction to the nervously exhausted patient who consults us for aid, let us investigate his problem more carefully and see in what manner we can be of help to him.

A critical observer can sense after a few words with the patient that his confidence is shaken and that he is very much in need of a sympathetic ear. The examining physician will do well to allow him to tell his story without unduly hurrying him by direct or leading questions. Careful attention should be paid to the symptoms that are uppermost in the patient's mind; usually a good insight into the emotional state, and especially about the fears, can be gained in this.

The complaints of these patients are legion. They all complain of exhaustion and easy fatigability. Many are blue, melancholy, and depressed with fears for their sanity. They are restless, irritable, and unable to relax. Insomnia is almost the rule. Memory is usually poor, especially for names, and it is difficult for them to concentrate. They notice particularly that it is difficult for them to read and concentrate on

a subject. It becomes increasingly difficult to make decisions and have confidence in the correctness of the decision. People and especially crowds make them very nervous and they prefer not to see people although they frequently desire the companionship of some very close friend in order to avoid being entirely alone. They are extremely sensitive to the slightest personal remarks which often are greeted with outbursts of tears.

All kinds of peculiar bodily feelings occur. They have drowsy feelings, creepy feelings, band-like feelings in the head, stupid feelings, dizzy feelings, and many others. The top of the head, the back of the neck, and the region of the throat are favorite locations in which tight feelings or a feeling of pressure occur. We have had an opportunity to study a great number of patients who complained of peculiar subjective disturbances in the throat which they feared were caused by goiter. A sense of heaviness in the chest and deep sighing respirations are almost pathognomonic of a depressed emotional state. Precordial distress and cardiac palpitation become a source of great fear. All types of digestive symptoms appear. The disturbed appetite leads to faddish diets and deficiency states. The rectum and sex organs are not uncommon sites for vague subjective feelings. Other symptoms too numerous to mention could be detailed, but these are usually sufficient to give the examiner a good clue into the nature of the trouble before the patient finishes his story. It is only the unwary who will expose his hand at this time and try to argue with and convince the patient that he has no organic ills to account for his trouble. The wise physician will make careful inquiry into those regions and domains that seem of greatest concern to the patient.

A physical examination should be performed in a thorough and routine manner and all possible clues to disease should be elicited. It is curious how frequently the patient will reveal, during the examination, his secret fears of disease by being overanxious about the examiner's findings in the domain of his interest.

Foci of infection, evidences of glandular derangement, evidence of mineral and vitamin deficiency, and organic disease of the nervous system should be the chief object of search as the examination is conducted. Laboratory investigations, roentgen studies, and consultations in special fields are almost indispensable in these problems. The teeth, tonsils, and sinuses should be thoroughly investigated for foci of infection. The prostate is frequently overlooked as a source of infection that frequently is most devitalizing to the patient. Errors of refraction and muscle balance should be ruled out as a cause of fatigue and a thorough examination of the eye is of great value to rule out intracranial lesions. A determination of the basal metabolic rate will differentiate the occa-

sional cases that are confusing in the diagnosis of hyperthyroidism. It is very difficult to differentiate hypothyroidism, because practically every patient in a state of nervous exhaustion will have a very low basal metabolic rate. Such a finding must not be immediately interpreted as one of hypothyroidism. In many cases only a carefully controlled therapeutic test with thyroid extract will differentiate the exhaustion of thyroid deficiency from nervous exhaustion.

The fears of the patient, more often than the concern of the physician, require that roentgen examination of the chest and electrocardiograms be made. Roentgen examination of the gastro-intestinal tract is made only in those patients having digestive symptoms. A spastic, irritable colon is almost universally found in the nervous patient. Cancerphobia, especially fear of cancer of the stomach, is so prevalent that roentgen examination of the gastro-intestinal tract is invaluable as a psychotherapeutic agent. Care must be taken in interpreting the significance of nonfunctioning gallbladders. For some unexplainable reason it is not uncommon to find a nonfunctioning, or poorly functioning, gallbladder in a highly nervous patient with marked symptoms of dyspepsia. A repetition of the examination after a brief period of rest and treatment will frequently show a complete return of function of the gallbladder. I have found the Ewald meal to be of inestimable value. Achlorhydria and its significance in possible deficiency states has often been the directing clue to the correct replacement therapy in patients who otherwise appear to be nervously exhausted. The pelvis has been the happy hunting ground of the surgeons to explain many of the nervous ailments of women. Medical gynecologic treatments, plastic operations, suspension, and total or partial ablation of the ovaries are usually of no value in the treatment of nervous disorders and the results are frequently more harmful than good. Routine examination of the blood and urine and complement fixation will reveal the true nature of many unsuspected diseases. Many observers have reason to believe that undulant fever in its chronic form, chronic brucellosis, may be the explanation of the symptoms of many patients suffering from chronic exhaustion. In such cases it is well to test for this disease, but unfortunately the tests are unsatisfactory in determining to what degree this condition accounts for the patient's symptoms even if there is a positive reaction. Furthermore, treatment, for the most part, has yielded such discouraging results that this diagnosis has been more discouraging than encouraging to the patient.

Innumerable chronic disease states may devitalize the patient, producing the general symptoms of exhaustion rather than the outstanding symptoms of the disease. Many such diseases will remain undiscovered because of lack of sufficient localizing symptoms; it is important to re-

examine these patients periodically with a fresh viewpoint if the response to therapy is not satisfactory.

After the examination has been completed to the satisfaction of the patient and the examiner, the most difficult problem of therapy begins.

If the patient is satisfied that the examination is complete and thorough, and especially that his fields of particular fears have been thoroughly studied, he is usually satisfied with the statement that no disease exists which accounts entirely for his trouble. He must be convinced that his symptoms are predominantly due to poor function of all the organs of the body because of a devitalized central energy station. If some minor foci or other disease processes are found, he can be told that they have contributed to his loss of energy but that their correction is not the sole answer to his problem. Even though they are a major contributing factor, their removal will still leave him in the same exhausted state that only the energy-building processes of nature, rest, relaxation, food, sleep, confidence, and happiness will restore.

As mentioned previously, if the treatment of disease is likely to be extremely devitalizing, it had better be postponed. Frequent talks with the patient to bolster up his waning confidence and especially to explain, in a way that allays rather than increases the fear, the reason exhaustion can cause all his symptoms is the most helpful type of psychotherapy. A patient left alone too long with his own thoughts slowly reverts to all the fears that the original examination may have allayed.

New symptoms arise to replace the old ones and these must continually be combatted with ready explanations. The slightest expression of anxiety on the part of the physician is multiplied many times in the patient's mind.

The patient must be cautioned that the loss of energy has been slow and over a much longer period of time than he believes. Likewise, he must be told that the restoration of energy will be slow and the period of treatment must extend long after he believes himself fully recovered if a reserve of energy is to be built up to carry him through any unusual strain; otherwise he will surely have a recurrence. He must also be warned that his energy budget must be balanced after he recovers and that consumption must not exceed production. Inevitably he will have a recurrence if he does not get more rest and do less work than he did prior to his illness. The milder cases may be treated without a period of complete rest; but if rest is advised it should be sufficiently long to restore the patient completely or it is a loss of the patient's time and money. It is extremely discouraging for the patient to be advised to go to Florida for a month only to find on his return that he is no better. Frequently a patient will even be much worse after several weeks or a month of rest.

This can be explained to him, or even predicted, on the basis that as he relaxes he will feel even more exhausted. It must be explained that this was only his real condition prior to rest and his small output of energy was only being kept up by constant unwise stimulation. Economically, it is better for these patients to rest voluntarily a shorter period of time at the beginning of their trouble than to be forced to give up completely for a longer period of time later on, because this frequently results in loss of their positions.

Specific vitalizing agents are next to useless. A condition in all respects similar to nervous exhaustion is seen at the menopause which frequently shows startling results following endocrine therapy. I firmly believe that we may expect new additions to our endocrine armamentarium in the future which may be helpful in similar conditions other than at the menopause. The cyclic fatigue and nervous states which so frequently accompany the menses and completely disappear during pregnancy, and the postpartum exhaustions should eventually be solved on a glandular basis.

All types of symptomatic therapy should be practised, especially with a view to better sleep and a better nourished state. Physiotherapy and hydrotherapy are especially valuable. The undernourished patient should receive extra calories in frequent feedings, the gastro-intestinal symptoms should be relieved, and as this is most frequently due to a spastic colon, laxatives should be eliminated and normal bowel function restored. This may follow any of the rational treatments for irritable colon. Obese patients do better with restriction of food. A reduction in weight should be slow and preferably it should be accomplished by means of a well-balanced diet with sufficient vitamin and mineral constituents. Deficiency states are much more prevalent than is supposed and they are not an unimportant factor in the nervously exhausted patient. Because of digestive disturbances these patients frequently limit their diets. The teeth often have been the first object of suspicion and their removal has further restricted the diet, especially the intake of the valuable protein foods. While vitamin therapy is unquestionably much overdone, there is nothing to replace it when actually needed.

Insomnia is the most troublesome of all symptoms and its treatment would require a discussion longer than space permits. Sedatives are allowed when necessary, but their excessive use should be discouraged, especially in the older patients whose tolerance is often exceedingly small. Not infrequently an increase in the patient's psychic symptoms is due entirely to overuse of sedative drugs. Slight sedation throughout the day is often of more value in obtaining relaxation and sleep than knock-out doses at night which cause a hangover the following day. All psychic

and other well-tried methods of obtaining sleep are preferable to complete reliance on drugs.

Every patient is a problem unto himself, and the solution requires much time, patience, and ingenuity on the part of the physician. Any discussion of treatment will always be inadequate to cover the specific details in all cases.

There is just one final admonition in regard to treatment that I believe should be enforced in all cases. Almost universally the rule with relatives and friends and only too often the advice of physicians is to urge the patient to do things which he previously liked, but now finds very difficult and extremely fatiguing. This especially applies to his routine duties and social relationships with his friends. He would prefer not to see people and must constantly force himself to perform his usual duties. He is afraid he will be considered lazy and continues to force himself for this reason. Well-meaning friends and relatives devise all manners of stimulating activities to revive his waning interest in life. I firmly believe that this disinterest in life is Nature's way of effecting a rest cure and that further stimulation of any sort is to be strictly avoided. I advise these patients never to do anything they do not want to do and to carry out only a fraction of the activity some revived interest may incite them to want to do. It should be made clear to the patient and to his relatives that it is entirely contrary to the nature of these patients to be lazy and that only by catering to the desire for rest can he be restored to normal activity. Crowds and people above all other things are exhausting to these patients. The fight between being bored to death by rest and tired to death by activity requires very great consideration, and when a patient cannot be placed in a well-managed sanatorium where this is all provided for, the problem is a big one. It must be solved in each individual case by the limitations of the patient's environment.

The prognosis is almost universally good in the young patient, but this decreases with increasing age and the frequency and severity of the attacks—a very important point in the history for both diagnosis and prognosis. Once a patient has suffered an attack of nervous exhaustion he is never free to follow the dictates of his own will and desires, but if recurrences are to be prevented his life should be regulated almost as carefully as the highbred race horse's life is governed by his trainers. Each succeeding recurrence is more severe, lasts longer, and the recovery is less complete.

Endeavor, if the patient feels you have been responsible for his recovery, to have frequent conferences with him so that you may act as his conservator of energy. These patients have a natural tendency to recover and if the physician is fortunate enough to see them at, or near,

the natural time for this improvement, he receives great credit regardless of his mode of therapy. Woe unto him, however, if the patient has another relapse. The treatment which was hailed as so marvelous will surely fail to give the same quick response a second time, and the patient must go through another period of energy upbuilding.

Finally, the patient should be strictly cautioned as he approaches recovery. He must be warned that he will have occasional good days on which he will almost surely commit some foolish overactivity unless he is specifically told that such days are only a beginning of recovery and that rest on these days will be much more advantageous in hastening his recovery.

A CASE ILLUSTRATING THE ANALOGY BETWEEN ESSENTIAL HYPERTENSION AND RAYNAUD'S AND BUERGER'S DISEASE

GEORGE CRILE, M.D.

The patient was a man, 42 years of age, who was admitted to the Cleveland Clinic, April 30, 1937, with the complaint of pain in the fingers and toes of 15 years' duration. In addition to the pain, he had had numbness and tingling in his fingers. The symptoms were intermittent, but progressive in nature, so that he had been unable to work for five years. For three and one-half years, he had had severe paroxysmal pain in the finger tips which felt "glassy" and were very sensitive to pressure. He had resorted to morphine for relief of the pain. He stated that his fingers would become white, then red, and then blue, and that they were "ice cold" at times, even in hot weather. Partial relief could be obtained by plunging the hands into cool water. Exposure to cold produced numbness and a loss of sensation in both the hands and the feet. Because of gangrene, the right middle finger had been amputated in 1934 and the left middle finger in February, 1937. The patient is of Irish descent.

There was nothing of significance in the past history. Physical examination revealed a well developed male who was fairly nourished; height 67 inches, weight 153 pounds. The temperature and pulse were normal. The blood pressure in millimeters of mercury was 120 systolic, 70 diastolic. The skin over the hands and feet was moderately flushed, shiny, and somewhat atrophic. There were patchy areas of brownish pigmentation over the feet, ankles, and lower legs. The middle finger of each hand had been amputated (Fig. 1).

FIGURE 1: Photograph of patient's hands.

The radial pulses were of fair volume. The dorsalis pedis pulse was barely palpable in the right foot and was not palpable in the left. The posterior tibial pulse was not palpable in either foot. Popliteal pulsations were present on both sides.

The laboratory findings were as follows: urinalyses, negative; blood count, 3,700,000 red blood cells, 6,300 white blood cells; hemoglobin, 84 per cent; fasting blood sugar, 66 mg. per hundred cubic centimeters; blood urea, 33 mg. per hundred cubic centimeters; the blood Wassermann and Kahn tests both gave negative results.

A diagnosis of Raynaud's disease was made.

A left celiac ganglionectomy, division of the remaining nerve supply to the adrenal gland, and division of the lumbar sympathetic chain were performed May 3, 1937. The ganglion weighed 1010 mg.; the average normal weight of the left celiac ganglion in the male is about 340 mg.

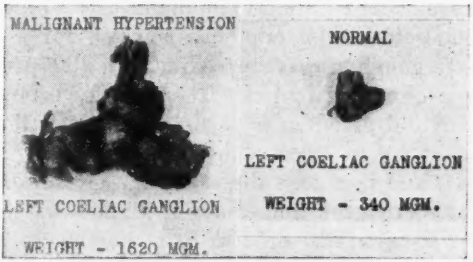

FIGURE 2: Celiac ganglion in case of essential hypertension.

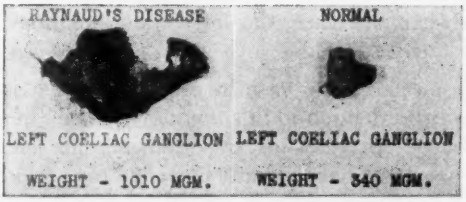

FIGURE 3: Celiac ganglion in case of Raynaud's disease.

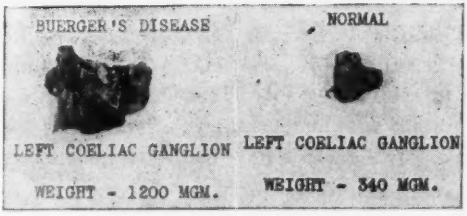

FIGURE 4: Celiac ganglion in case of Buerger's disease.

Immediately after the operation, the pain disappeared from the extremities and they were no longer sensitive to pressure. Examination of the hands and feet on the day of the operation showed them to be warm, pink, and dry. The skin temperature of the extremities was taken repeatedly by Dr. Zeiter under controlled conditions and showed a more constant elevation than was present before the operation, the average readings being about one to one and one-half degrees higher.

A right celiac ganglionectomy and division of the splanchnic nerves was performed May 17, 1937, and was followed by a good recovery. The ganglion on this side weighed 535 mg.

The skin temperatures have been more constantly elevated with less variation since the second operation. There has also been a marked change in the general appearance and disposition of the patient since he has been relieved of his pain and anxiety.

Comment: In this case, complete relief from the symptoms of Raynaud's disease occurred almost simultaneously with the completion of the first operation. This relief has endured for a period of six weeks. The left ganglion was approximately 300 per cent heavier than the average normal ganglion. The analogy between the hypertrophy of the thyroid gland in hyperthyroidism and the hypertrophy of the celiac ganglion in essential hypertension (Fig. 2), Raynaud's disease (Fig. 3), and Buerger's disease (Fig. 4), and the fact that in many cases of hypertension immediate relief follows celiac ganglionectomy make it seem worth while to call attention to the possibility of attacking Raynaud's disease and Buerger's disease by excision of the celiac ganglion. This operation has been performed in a case of Buerger's disease in which relief has already persisted for a period of three months. In this case, the left celiac ganglion weighed 1200 milligrams.

The reason for reporting a case in which operation was so recently performed is to call attention to this analogy between hypertension and Raynaud's disease. In cases of hypertension, the beneficial results of celiac ganglionectomy have already persisted for periods of more than a year. The permanence of the result in this case remains to be disclosed.

SOME ENDOCRINE AND RELATED FACTORS INFLUENCING SPERMATOGENESIS

WILLIAM E. LOWER, M.D., EUGENE CUTULY, PH.D., AND D. ROY MCCULLAGH, PH.D.

In the last two or three decades, important papers have appeared concerning the effects on spermatogenesis of diet including vitamins, of bacterial toxins, of alcohol, of tuberculin, of vasectomy, of testicular transplantations, of radiation of light, of seasonal rhythms, of sexual excess, of venereal disease, and of age, but a complete review of the literature is impossible here. The purpose of this report is to summarize some of the results of recent studies on experimentally induced testicular atrophy and repair and to indicate the possible value of such findings clinically.

HYPOPHYSECTOMY

That gonadal activity is dependent on the anterior lobe of the pituitary gland has been known since Crowe, Cushing and Homans[1] performed their notable experiments on dogs. They demonstrated that removal of the posterior lobe of the pituitary gland did not influence the genital development of dogs but that complete removal of the gland resulted in an atrophic condition of these organs. Some investigators have claimed that the genital atrophy following hypophysectomy is due to brain injury. Although brain injury may influence the genitalia, there now remains no question but that prehypophyseal hormones are necessary for normal gonadal activity.

A great portion of our knowledge concerning the effects of hypophysectomy has been the result of observations on the rat, commencing with the classical work of Smith[2]. If male rats are hypophysectomized before puberty, they never become sexually mature. The accessory sex glands remain infantile in appearance and the testes decrease in size. Spermatogonia and Sertoli cells remain normal in appearance but spermatogenesis does not occur. If the operation is performed after maturity, a similar picture results. The testes become greatly reduced in size and much less firm in consistency. Spermatozoa, spermatids, and spermatocytes rapidly disappear from the seminiferous tubules. Sertoli cells and spermatogonia remain, the latter continuing to undergo mitotic division for months after the operation.

As pointed out by Smith[3], destruction of the seminiferous tubules frequently is accompanied by a relative, though not absolute, increase

in the cells of Leydig. Following hypophysectomy, however, the Leydig cells become atrophic in appearance and the testes no longer produce male sex hormone as evidenced by the fact that the accessory sex glands become markedly atrophic. These degenerative changes following hypophysectomy always occur very rapidly following the operation, being noticeable five days later and almost complete in 18 days. In Table 1 the weights of organs of normal rats and of rats

TABLE 1

Average Weight (Grams) of Rats Hypophysectomized for 18 Days and of Rats Hypophysectomized and Treated with 1.5 mg. Androsterone Daily for 18 Days.

	Normal Control	*Hypophysectomized Control*	*Hypophysectomized Treated*
No. of Animals	8	4	7
Testes	2.41	0.54	1.57
Seminal Vesicles	0.745	0.096	0.431
Ventral Prostate	0.325	0.034	0.239
Dorsal Prostate	0.185	0.042	0.139

hypophysectomized for 18 days are compared. There can be no doubt but that the hypophysectomized rats were lacking in male sex hormone. The importance of this will be discussed later.

Recently, studies have been made of the scrota of hypophysectomized rats. We have shown[4] that the scrotum behaves as do the other accessory sex organs in that it rapidly regresses following hypophysectomy. About one week following hypophysectomy, the scrotum has greatly decreased in size and we believe this to be due, in part at least, to lack of male sex hormone. Hamilton[5] has also adduced evidence indicating that the scrotum is controlled by male sex hormone. Following hypophysectomy, one of the first observable signs of abnormality in the male rat is the disappearance of the testes from the scrotum about ten days after the operation. Our observations have led us to believe that this is not the result of pressure caused by the regressing scrotum but is an actual ascent of the testes into the abdomen.

CRYPTORCHIDISM AND HEAT

It has long been known that in man and most other mammals spermatogenesis does not occur unless the testes occupy a scrotal position. Outstanding among the contributions on this subject are those of Moore and his associates. The subject has recently been reviewed by Moore[6]. Cryptorchidism does not significantly interfere with the

power of the testes to maintain the accessory sex organs for at least a period of months. This is true even when very young animals are made cryptorchid by surgical means—normal sexual development occurs but the spermatogenic elements fail to mature or function. When adult rats or guinea pigs are made cryptorchid, the seminiferous tubules undergo amazingly rapid degeneration so that, at the end of a week or ten days, no spermatozoa and rarely spermatids can be found. Later, even the spermatogonia disappear and only Sertoli cells remain. The testes become very small and flabby. As long as spermatogonia exist, recovery of spermatogenic function will take place if the testis is brought into the scrotum.

Moore has been able to prove quite conclusively that, in those animals in which spermatogenic activity requires the scrotal position of the testes, the scrotum acts as a thermoregulator and that its influence on spermatogenesis is due to this property. The nature of the scrotum is such that its temperature is always several degrees lower than the intra-abdominal temperature of the animal. If the scrotal temperature is artificially increased, the epithelium of the seminiferous tubules is partially or completely destroyed. Insulation around the scrotum sufficient to force the temperature to that of the adjacent tissues will cause testicular destruction. Temperatures slightly above body heat will cause tubular damage in a few minutes.

The reason for the survival of the testes in the abdominal cavities of some mammals is unknown. It may be that a more complete investigation of the changes in body temperature will throw some light on the subject. A recent and interesting investigation by Riley[7] on the diurnal nature of spermatogenesis in the sparrrow indicates that short periods of low temperature may be of considerable importance in spermatogenesis in certain species. In the sparrow, the temperature varies from 110° F. during the day to 103° F. during the night. It is only during the period of lowered temperature that spermatogenesis occurs. If the light and dark of day and night be artificially reversed, the temperature of the bird is reduced during astronomical daytime and spermatogenesis proceeds during the afternoon.

The Injection of Pituitary and Pituitary-Like Hormones and Parabiosis

The question of the number and the nature of gonadokinetic hormones in the anterior lobe of the pituitary gland is one of the most controversial in endocrine literature. Whether or not any of these substances directly influence spermatogenesis remains open to question. There is, however, no doubt concerning the fact that the genital atrophy which occurs following hypophysectomy can be completely repaired by im-

plantation or injection of pituitary substance. This includes recovery of the ability of the testes to produce spermatozoa.

Unfortunately, from the point of view of the work under discussion, more investigation of pituitary-gonadal relationship has been made using female than male animals. Smith, in reviewing the subject of the gonadotropic hormones, is inclined to agree with those workers who believe that there are at least two gonadotropic factors—one the "follicle-stimulating" (FSH) and the other the "luteinizing" (LH) hormone. The names obviously are derived from the action in the female but it is believed by those who adhere to this idea that FSH acts as a gametokinetic hormone in both sexes and that LH stimulates the theca cells in the ovary and the interstitial cells in the testes. The experiments of Greep, Fevold and Hisaw[8] lend strong support to the view of the duality of pituitary gonadotropic function. Proponents of this idea also feel that nature has demonstrated a difference between gonadotropic hormones and that during the menopause and following castration the blood and urine contain largely FSH, probably of pituitary origin. It is also pointed out that the gonadotropic hormone of human pregnancy urine, although possibly not of hypophyseal origin, meets most of the requirements of a true LH.

In this laboratory we have carried out experiments designed to elucidate this problem more completely. Smith and Leonard[9] and Evans and his associates[10] state that the seminiferous epithelium is stimulated by extracts of pregnancy urine. This is denied by Collip[11]. We find that intensive treatment with pregnancy urine of hypophysectomized adult rats in which the testes have regressed will result in a limited degree of stimulation of the germ cell line. The bulk of evidence seems to show that pregnancy urine is not a pure interstitial cell-stimulating hormone (comparable to LH).

The problem of the type of hormone coming from the pituitary of castrated animals was next investigated[12]. The technic employed appeared to us to be as unequivocal as any available. In testing for any endocrine product, the most sensitive test animal is one from which the gland producing that hormone is removed. Therefore, in testing for gonadotropic hormone we used hypophysectomized animals. The problem of the frequency of treatment of the test animals was precluded by uniting them in parabiosis with the experimental animals and thus having a continuous administration of hormone. From the results of these experiments, there could be no doubt but that the pituitary glands of castrated rats produced a greater amount of gonadotropic substance than did those of normal animals. There was, however, no indication of any selective gametokinetic or interstitial cell stimulating activity.

THE INJECTION OF ANDROGENS

Effect of Injection of Androgens in Hypophysectomized Animals

For some time there has been no doubt that adequate doses of male sex hormone will prevent atrophy of accessory sexual organs in hypophysectomized as well as in castrated rats. Freud[13] demonstrated this in castrated hypophysectomized rats using hombreol or testicular extracts. Vatna[14] observed repair of the accessory glands of hypophysectomized rats using bull testis extracts but was unable to detect any repair of the testicular tubules if injections were begun three weeks after the operation. Walsh, Cuyler and McCullagh[15] studied the effect of androtin (fat soluble sex hormone of human male urine) on adult hypophysectomized rats and found that it prevented atrophy not only of the accessory organs but also of the testes. The urinary extracts were unquestionably free of pituitary or pituitary-like hormone. Nelson and Gallagher[16] recently confirmed this work and considerably extended it by demonstrating that urinary androgens would not only maintain the normal appearance of the testes of hypophysectomized rats over a very long period but that these rats were capable of siring normal litters. Nelson[17] has also shown that, in addition to androgens, progesterone possesses the property of maintaining spermatogenesis in the absence of the hypophysis and of hypophyseal hormones. Eight synthetic androgenic sterols* have been quantitatively investigated in this laboratory, the findings on only three of which have been reported[4]. The most important androgen in urine appears to be androsterone. Table 1 shows the effect of the injection of this substance into hypophysectomized rats. Although at this dose level (1.5 mg. daily), the testes of the treated animals were somewhat smaller than those of the normal controls, histological examination revealed normal spermatogenesis in the majority of the tubules. Using the weights of the prostate glands as a criterion of dose, these animals received only 75 per cent of a maintenance dose. Possibly with a larger dose there would be no signs of tubular degeneration. In this case, occasional tubules distributed throughout the whole of the gland showed signs of degeneration quite comparable to untreated hypophysectomized controls. Of the androgens so far investigated by us, the most efficient from the point of view of the maintenance of spermatogenesis in the absence of the hypophysis is dehydroandrosterone acetate. Spermatogenic stimulation under these circumstances is a common property in varying degrees of all androgens tested.

Maintenance of the testis tubules in hypophysectomized rats is not limited to pituitary extracts, pituitary-like hormones from urine, or

*Supplied through the courtesy of Dr. Erwin Schwenk of the Schering Corporation, Bloomfield, N. J.

gonadal hormones. Hisaw, Greep and Fevold[18] report that yeast extracts prevent degeneration of the seminiferous tubules of hypophysectomized rats. All substances which have been demonstrated to have this property also possess the property of maintaining the scrotum. This, of course, is to be expected since spermatogenesis cannot occur without the scrotum.

None of the androgens investigated have, as far as we can determine, prevented the usual atrophy of the interstitial cells of the testes in hypophysectomized rats. In this the androgens differ from the gonadotropic hormones. The indications are at present that there is another important difference between the effect of these two types of hormones. It has been noticed by Nelson[17] as well as in this laboratory that if the testes are permitted to regress following hypophysectomy the injection of androgens will not cause their regeneration.

Effect of Injection of Androgens Into Normal Male Animals Not Producing Spermatozoa

Moore and Price[19] showed that from 3 to 12 bird units of androgenic bull testes extracts led to a reduction in size of as much as 50 per cent in the testes of growing rats as compared to littermate controls. More recently, Moore and Price[20] showed that similar results were obtained when young rats were treated with androsterone. Wells and Moore[21] observed that in the ground squirrel (which is an annual breeding type as opposed to the constant breeding rat) a definite stimulation of spermatogenesis occurred following the administration of androgens from male urine and testes, as well as androsterone. During the first year of life, immature animals were caused to produce spermatozoa four months earlier than normal controls. The injection of androgens caused adult squirrels to produce spermatozoa normal in appearance and activity during seasons when they normally show no signs of testicular activity. One of the effects of the administration of androgens into sexually inactive squirrels was that the testes, which at that time are normally cryptorchid, descended into the scrotum. This may have been all that was necessary to cause spermatogenesis. Evidence is still lacking therefore that the androgens are directly gametokinetic.

Effect of Injection of Androgens Into Normal Adult Male Rats

At the present time, various androgens may be purchased for clinical use and further knowledge concerning possible undesirable reactions resulting from their administration seems to be indicated. This is particularly true when the problem of spermatogenesis is considered. It has been shown that androsterone produces a deleterious effect in young rats. The rapidity with which such animals recover from this

condition has not been reported. Moore and Price[20] showed that prolonged injection of large doses of androsterone into adult male rats did not have a deleterious effect upon the testes.

Androgens are known to depress pituitary activity. McCullagh and Walsh[22], using the parabiotic technic, injected urinary androgens into castrated rats and controlled the hyperactivity of the pituitary glands of the castrated animals. It seemed possible that large doses of androgens might depress the normal pituitary gland in such a fashion that, although no serious damage appeared during the course of the injection, hypogonadism of pituitary origin might result subsequent to the cessation of injections. For this reason, normal adult male rats have been

TABLE 2

Body and Organ Weights (Grams) of Normal Adult Rats Injected with Androstenediol (3 mg. in 0.5 cc. Sesame Oil) Subcutaneously Daily for 18 Days. Rats Were Autopsied at Various Intervals Following the Injection Period.

Final Body Weight	*Pituitary*	*Testes*	*Seminal Vesicles*	*Ventral Prostate*	*Days Autopsied after Final Injection*
274	.007	2.96	.728	.370	1
239	.008	1.98	1.455	.472	1
278	.007	2.82	.692	.272	1
266	.008	2.80	.814	.342	4
216	.006	2.59	1.265	.348	4
220	.008	2.74	.962	.500	6
182	.007	2.17	1.248	.671	6
275	.010	2.60	.762	.395	8
284	.008	2.33	.741	.349	8
243	.007	2.71	.578	.344	11
242	.006	2.69	.739	.406	11
287	.007	3.26	.574	.290	14
285	.008	1.38	.849	.287	14
219	.007	2.72	.468	.157	14
245	.008	2.84	.957	.381	18
262	.007	2.98	.611	.225	18
310	.010	2.71	1.111	.483	20
Uninjected Normal Controls (Average Weights for 8 Animals Sacrificed at Varying Periods During the Experiment).					
277	.008	2.85	1.026	.348	(4-20)

injected with large doses of androgens and subjected to necropsy at various periods after the last injection.

Table 2 shows the effect of the daily injection of 3 mg. of androstenediol for 18 days. By previous experiments, it had been ascertained that the dose of hormone would more than maintain the

accessory sexual glands of hypophysectomized or castrated adult male rats. The animals were sacrificed at periods varying from 1 to 20 days after the last injection. An examination of the weights of the organs indicates neither stimulation nor depression of the sexual glands.

TABLE 3

Body and Organ Weights of Normal Adult Rats Injected with Testosterone Propionate (1.5 mg. in 0.5 cc. Sesame Oil) Daily for 18 Days. Rats Were Autopsied at Various Intervals Following Injection Period.

Final Body Weight	*Pituitary*	*Testes*	*Seminal Vesicles*	*Ventral Prostate*	*Days Autopsied after Final Injection*
280	.007	2.52	2.220	.646	1
237	.007	2.74	1.859	.541	1
238	.007	2.84	1.909	.610	1
299	.008	3.06	2.194	.606	4
223	.006	3.14	1.666	.537	4
270	.007	2.63	1.989	.538	6
241	.007	2.24	1.351	.561	6
298	.007	2.54	.892	.346	8
204	.005	2.12	1.051	.325	8
213	.005	2.24	.882	.462	11
222	.007	2.18	1.112	.389	11
233	.007	2.69	.....	.391	14
233	.006	2.77	.942	.330	14
244	.007	2.51	1.357	.364	14
286	.007	2.60	1.082	.437	18
281	.007	2.89	1.322	.428	18
293	.009	2.41	.992	.467	20
218	.006	2.40	.705	.260	20
Uninjected Normal Controls (Average Weights for 9 Animals Sacrificed at Various Periods During the Experiment).					
241	.007	2.56	.923	.298	(4-20)

The experiment was repeated (Table 3) using the more potent compound testosterone propionate in doses of 1.5 mg. daily for 18 days. The animals were examined as in the preceding group. It had previously been determined that 1.5 mg. of testosterone propionate was not only more than sufficient to maintain the accessory glands of castrated rats but that it also caused marked changes in the pituitary glands. The weights of the organs do not indicate that the testes or pituitary glands were influenced in any way by this treatment.

The seminal vesicles and prostate were distinctly enlarged at the end of the injection period and returned to normal within twenty days. Had there been any marked hypofunction of the pituitary gland, the

curve of decrease in weight of the accessory glands would have been expected to be much sharper.

Discussion

It is well known that androgenic activity on the part of the testes is an essential factor in the care and transportation of spermatozoa from the time of their production to the time of their deposition in the female genital tract. Recent experiments show that androgenic activity is necessary for the production of spermatozoa. Our studies lead us to believe that the maintenance of the scrotum and the control of the factors which cause the testes to retain their scrotal position are dependent on the presence of androgens. As shown by the experiments on cryptorchid animals, these conditions are essential before spermatogenesis can proceed.

It remains to be determined whether or not androgens have a function other than the preparation of the stage for spermatogenesis. New experiments will have to be devised before it will be known whether or not androgens are directly gametokinetic.

The interpretation of the experiments concerning the rôle of the pituitary gland in the process of spermatogenesis is even more difficult. In the male it would seem that the most essential gonadotropic function of the pituitary gland is the stimulation of the interstitial cells of the testes. These cells produce androgens essential for spermatogenesis. The question then arises as to the reasons for postulating a gametokinetic activity on the part of the anterior lobe of the pituitary gland. The most important point experimentally is the fact that, by the use of androgens, it has been impossible to cause repair of posthypophysectomy atrophy of rat testes, whereas pituitary extracts will bring about this restoration. If one wishes to believe that the pituitary has no gametokinetic effect in the male rat, one can argue that the interstitial cell-stimulating hormone causes the testes to produce different and more effective androgens than those which we have injected. The existence of androsterone as well as testosterone indicates definitely the possibility that other intermediate androgens exist normally.

Because spermatogenesis cannot occur unless the testes are in the scrotal position, it is difficult to conceive that a purely gametokinetic effect may be demonstrated by the injection of pituitary preparations into male rats. Until new methods are available, it seems improbable that a final answer can be given to the problems suggested in this paper.

Sterility in the Human Male

Masculine ego has been blamed in part for the amazing lack of investigation into the responsibility of the male for barren marriages.

Although it has been recognized for years that potency did not indicate fertility, it is only within the last decade that serious efforts have been made to devise methods for the diagnosis and treatment of male sterility.

From the history and physical examination of a patient, facts of considerable diagnostic value may be garnered. The most valuable criterion, however, of fertility is to be found in the examination of the semen. This requires considerable experience and skill. The diagnosis of fertility by glancing down a microscope and seeing a few motile spermatozoa in a condom specimen is worse than useless in that it misleads both patient and physician. Hotchkiss[23] outlines the most essential points in the technic of sperm analysis; Moench[24] has investigated the problem of thorough examination of semen; methods are available for making accurate counts of the sperm; and technics for collecting and staining for proper examination of motility and morphology may be found in the literature. Just as proper methods must be used in hematology and other laboratory work, they must also be employed in the examination of semen.

When examination of the semen indicates low grade fertility or sterility, that does not constitute proof of any endocrine disorder nor is it necessarily an indication for endocrine therapy. Various other influences such as those mentioned in the introductory part of this paper should be considered and, so far as possible, corrected or ruled out as contributing factors to the inadequacy of the semen. If, however, there is still reason to suspect that the condition is of endocrine origin, further studies should be made to ascertain the nature of the endocrinopathy. In this regard, biological assays of blood and urine for sex hormones may be of considerable value. In primary testicular deficiency, the decrease in the production of androgens is frequently accompanied by increased gonadotropic activity. If the hypogonadism is of pituitary origin, there is also a decrease in output of androgens but never an indication of increased gonadotropic hormone.

When lack of fertility can be shown to be of endocrine origin, the prognosis is not particularly good. Chute[25] has recently summarized the problem of endocrine factors in human male sterility and correctly feels that many therapeutic failures have been due to indiscriminate and unscientific use of endocrine products. For example, there seems to be little reason for the administration of pituitary hormone to individuals who already excrete an excess of that substance. This type of therapy should be applied only when there is good reason to believe that the pituitary is deficient. Some authors report salutary effects in sterility by the use of pituitary-like hormone from urine and others have been very disappointed in this form of therapy. Possibly, gonado-

tropic preparations from pituitary glands will prove to have a greater gametokinetic effect.

The indiscriminate use of androgens is to be discouraged and numerous warnings have appeared in the literature. In view of recent researches, however, the statement that the gonads cannot be stimulated by androgens must be reconsidered and cautious clinical trials in appropriate cases by experienced endocrinologists would not seem to be contraindicated.

In the treatment of sterility of endocrine origin, the general health of the patient must be considered and the thyroid gland must not be overlooked. It is improbable that the thyroid hormone exerts any specific influence on the gonads; nevertheless, thyroid therapy is indicated when it is well tolerated by the patient.

Summary

Removal of the anterior lobe of the pituitary gland in rats results in cessation of the androgenic and reproductive functions of the testes. In hypophysectomized rats, the androgenic activity of the testes can be maintained or revived only by anterior pituitary (AP) or anterior pituitary-like (APL) hormones. Spermatogenic activity in hypophysectomized rats, however, can be maintained, if treatment is begun shortly following hypophysectomy, by a variety of substances: androgenic products, progesterone, and yeast, as well as by AP or APL hormones. On the other hand, if treatment is postponed for a considerable time following hypophysectomy, it has been found that only AP substance can restore gametogenesis to a completely normal condition. Regardless of the type of stimulation needed to maintain or revive spermatogenesis in the rat, it has been shown that this function can occur only if the testes occupy a scrotum which can exert a beneficial thermoregulatory effect. Recent studies have shown that such scrotal function is at least in part controlled by the male sex hormone. The significance of this observation is discussed with reference to the importance of androgenic activity to spermatogenesis, and to the difficulty encountered in postulating the existence of a pure hypophyseal gametogenic hormone.

Studies in normal adult rats have indicated that rather large doses of androgenic substances administered daily for 18 days failed to have any macroscopically visible deleterious effects on the testes, sexual accessory organs, or pituitary gland during, or as late as 20 days following, the injection period.

Sterility in men is discussed in the light of recent experimental findings. While caution is urged in the employment of hormonal therapy in

sterility, there would seem to be no objection in some instances to a judicious use of AP or APL hormones, as well as of androgenic substances.

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NEURALGIA OF DENTAL ORIGIN*

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Many methods have been advocated down through the years for the relief of pain in the head but less consideration has been given to the etiologic factors involved. Trephined skulls of ancient people have been uncovered and it has been assumed that operations were performed to allow confined demons to escape. Drugs also were used for the relief of headaches, and, in the Ebers Papyrus, frankincense, cumin, and goose grease are mentioned as specific remedies. These empirical methods, however, were gradually replaced when rational and scientific thinking directed efforts toward elimination of the causative factors. During this period, the teeth assumed increased importance in regard to etiologic factors; indeed, at times, they were given a place of too great prominence. The studies in 1829 of Sir Charles Bell were of great importance and to him we are indebted for an understanding of some forms of pain in the head, particularly of facial neuralgia which is due to disorders of the fifth rather than of the seventh nerve as was previously thought.

The anatomical relationships of the fifth nerve, which is the largest of the cranial nerves, are interesting in relation to the problem of pain in the head. This is the great sensory nerve of the head and face and the motor nerve of the muscles of mastication. The trigeminal nerve emerges from the lateral aspect of the pons, near its upper border and courses forward to the apex of the petrous portion of the temporal bone where it forms a large ganglion. The motor root passes beneath the gasserian ganglion to transmit motor impulses to the muscles of mastication. Three large branches are given off at this point. The ophthalmic branch is the first and smallest of the three; it passes anteriorly through the middle fossa and is located beneath the dura mater, making its exit from the cranial cavity through the superior orbital fissure. Before it emerges, however, it gives off communicating branches to the oculomotor, trochlear, and abducens nerves. Its terminal branches consist of the frontal, lacrimal, and nasociliary.

The maxillary nerve, or second division, is a sensory nerve. From its origin in the ganglion, as a flattened plexiform band, it passes forward horizontally, leaving the skull through the foramen rotundum. In crossing the pterygopalatine fossa, it gives rise to two of the smallest nerves of the body, connecting with Meckel's ganglion; it then enters the orbit through the inferior orbital fissure. Thence it transverses the

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infra-orbital groove and canal in the floor of the orbit and appears upon the face at the infra-orbital foramen. Its terminal branches spread out upon the side of the nose, lower eyelid and upper lip, joining with filaments of the facial nerve. Immediately before and during the passage of the nerve in the infra-orbital canal, it gives rise to three branches forming a so-called outer nerve loop which supplies the teeth and soft tissues of the buccal mucosa. The nerves arising from Meckel's ganglion, which has a communicating branch to the facial nerve, course forward and downward to form an inner nerve loop which supplies the hard and soft palate, the nasal tract, and the tonsillar fossa.

The third division or mandibular nerve supplies the teeth and soft tissues, the skin of the temporal region, and the lower part of the face including the lower lip and anterior two-thirds of the tongue. It is the largest of the three divisions and is made up of two parts, a large sensory and a small motor root. The two parts unite after passing through the foramen ovale. A small branch goes to the internal pterygoid muscle. It there divides into an anterior and posterior trunk. The anterior division supplies the muscles of mastication. The posterior is the larger and for the most part sensory, receiving a few filaments from the motor root. It subdivides into the auriculotemporal, lingual, and inferior alveolar nerves. The auriculotemporal branch winds around between the condyle of the mandible and the stylomandibular ligament, anterior to the external auditory canal. It is believed that this nerve is often involved in dyscrasias of the temporomandibular articulation. It is this intricate interrelationship which often makes the etiology of neuralgia difficult to trace and discover.

The symptoms of neuralgia are commonly divided into two groups, according to the intensity of subjective symptoms and clinical manifestations. Tic douloureux has been described as an acute, intense, sharp, sudden paroxysm of pain which emanates from a trigger zone and leaves the patient quite exhausted after the period but apparently free from further discomfort until the next attack. While the etiologic factor cannot be demonstrated, medical and surgical treatment is available which relieves the condition. In atypical neuralgia, the symptoms are much less severe and consist of a dull burning, boring, or throbbing sensation of a continuous nature. Very often the continuous factor of the discomfort appears to be more important to the patient than the actual pain. In this group more definite etiologic factors may be demonstrated, but this is not always true. It is in such cases that the teeth may be a factor. Other factors which must be considered are sinusitis, foreign bodies, malignancies along the pathway of the fifth nerve, disorders of the

temporomandibular articulation, involvement of the nerve pathway by sclerotic bone, galvanism, and those disorders not demonstrable clinically such as a neuroma and possible sclerotic nerve tissue which is the result of injection of a local anesthetic into the nerve trunk proper.

The intimate relationship between septic teeth and general symptoms including headache and facial neuralgia has been established. Two distinct types of pain may be associated with septic teeth and their investing tissues—neuralgia or odontalgia, a referred pain, and localized pain.

Neuralgias referable to the teeth or odontalgias may involve one or more branches of the trigeminal nerve and, when such symptoms are present, clinical and roentgen examinations usually show definite evidence of pain-potential teeth. In the presence of infection of the pulp, the pain at the onset and throughout the various stages of pulpitis, is usually of a general reflex variety, involving all the teeth in the region supplied by that particular branch of the fifth nerve. Pain may also be referred to the other branches but, in this case, it is always unilateral. The neuralgia, a primary odontalgia, becomes acutely intense and is localized to a particular tooth when the inflammation includes the entire pulp tissue. Such inflammation is followed by a necrosis ending in a putrefactive process with the formation of ammonia, carbon dioxide, hydrogen sulfide gases, peptones, ptomaines, and aromatic and fatty acids as the end products.

At this stage, heat and cold therapy are of little value. Heat actually may increase the symptoms, and reclining also tends to make the pain more severe. Direct relief can be afforded only by making an opening into the tooth to expose the pulp tissue and release the pressure. As the gangrenous process gradually progresses to involve the apical tissues, a second type of pain is evidenced. This is more of a continuous pain which increases with pressure due to mastication and it is confined exclusively to the affected tooth which often feels extruded from the socket. Such pain is a definite indication of involvement of the peridental membrane and periapical tissues. Brashear[1] has recently pointed out that pain sensation is peculiar to the pulp of the tooth, while pressure sensation is registered entirely by the investing peridental membrane. The latter type, or localized pain may also be experienced as the organisms reach the periapical tissue by way of the surrounding periodontal tissues as in pyorrhea alveolaris.

Percussion is a most useful diagnostic sign in the early stage, vitality testing is of some value, and the roentgenograms may show the beginning of periapical change.

The occurrence of a secondary pulpitis with neuralgia is not rare.

In the majority of cases, the underlying disturbance is due to infection such as acute nasal catarrh involving the antrum or other general diseases which affect the mucous membrane of the nose and the circulation as a whole. General diseases of noninfectious type such as leukemia, locomotor ataxia, anemia, chlorosis, or increased intradental blood pressure should be considered. Many sound teeth have been sacrificed because of this condition. A chronic dental septic condition in which no local subjective symptoms are present should always be considered in migraine headaches. The lessened virulence of the organism and resistance of the host precludes an acute attack, but the dissemination of toxic material, i.e., ptomaines and bacterial proteins, through the system may result in tissue sensitization or manifestations of allergy which may be responsible for a chronic headache or neuralgia.

Pulp stones are sometimes considered as etiologic factors in head pain of dental origin. I do not believe that pulp stones *per se* are the cause of neuralgia, because their presence can be demonstrated too frequently even in perfectly sound teeth and when no symptoms of neuralgia are present. If the entire histories were carefully reviewed in those cases of relief attributable to the removal of pulp stones, it would probably be shown that the questionable teeth contained fillings or had given some discomfort previously; in other words, they would fall under the classes already described under septic teeth. Hatton and others[2] have demonstrated the presence of pulp abscesses or circumscribed, walled-off areas of infection in otherwise normal pulps. Such teeth respond to the vitality test, appear negative especially to roentgen study, but usually show a large restoration which approximates the pulp, and pulp stones are present. These workers believe this condition is the only primary source of dental focal infection and is more prevalant today due to the overzealousness on the part of the dentist to prevent devitalization or loss of the tooth.

All the symptoms of neuralgia which originate from the dental structure as the result of irritations of the fifth nerve do not necessarily develop from dental sepsis.

Traumatic occlusion in conditions where the teeth have been lost gradually and have not been replaced may possibly result in neuralgia referable to teeth if unusual stress is placed upon them. It has been estimated that a leverage of 250 pounds per square inch can be exerted on the teeth by the muscles of mastication. The leverage on teeth weakened by loss of adjacent members results not only in neuralgia but in abnormalities of the fundamental structures as evidenced by drifting or tipping of the teeth. This naturally has a tendency to increase the pain, and the tooth may subsequently be lost due to weakened founda-

tion, or the impaired nutrition of the tooth may result in a devitalized pulp.

Where direct pressure, such as that due to an impacted tooth, a supernumerary tooth, an osteoma, or a cyst, is exerted at a foramen or directly on the mandibular canal, all the symptoms of neuralgia may follow. Main[3] cites the case of a man 50 years of age who had almost complete relief from chronic headaches following removal of an impacted cuspid. In one of our cases, the removal of an unerupted cuspid in the upper left arch resulted in relief of a dull occipital pain that had persisted over a long period of time. Main has demonstrated the relief of some cases of otalgia by the removal of unerupted and impacted lower third molars, and the relief of headaches by the removal of supernumerary teeth. He points out that unerupted upper third molars apparently have little bearing on neuralgia, but that the lower third molars may often be the etiologic factor. This is due to their proximity to the mandibular canal.

The following six cases illustrate these etiologic factors.

Case 1: A woman, 50 years of age, presented herself for roentgen study of the jaws. For many years she had experienced a sharp, stabbing, paroxysmal type of pain and a diagnosis of true tic douloureux had been made although there appeared to be no definite trigger zone. Both arches were edentulous, the teeth having been removed in an effort to lessen the pain.

Radiographic examination disclosed an unerupted lower right bicuspid lying horizontally in the mandible in close approximation to the mental foramen. In removal of the tooth, the mental foramen was uncovered and the mental nerve exposed due to the marked alveolar bone resorption that had occurred.

Following the removal of this tooth, there appeared to be complete relief from symptoms. This was so pronounced that shampoos no longer gave any uncomfortable reaction, although they formerly had caused severe pain which closely simulated the form of trigger zone stimulae.

Case 2: A man, fifty years of age, had been wearing dentures for many years, but for several months preceding our examination he had had a dull, throbbing pain in the lower left mandible. Examination revealed a small, hard, smooth surface in the region of the ramus, and roentgen examination disclosed an unerupted third molar and a residual area in the bicuspid region on the same side. Following the removal of the tooth and the residual area, the symptoms disappeared.

Case 3: A woman, 35 years of age, complained of neuralgia behind the ear and in the ramus of the left jaw. This pain at times appeared to center in the lower left second molar which was a crowned tooth and acted as a bridge abutment. Clinical and roentgen examinations of this tooth revealed no abnormalities. The persistent pain, however, prompted us to remove the bridge and crown whereupon the molar tooth was found to have extensive caries which apparently involved the pulp. The removal of this tooth eliminated the pain for a period of time, but several months later the patient returned with neuralgia of the left side of the face. Examination of the nose and throat gave essentially

normal findings as did a roentgen survey of the oral area. It was noticed that inflation of the eustachian tube gave some relief. Relief was also experienced when the vertical dimension of the relationship of the jaws was slightly increased, thus changing the temporomandibular articular relationship. Unfortunately, economic conditions were such that permanent measures were not adopted.

Case 4: A young woman, 25 years of age, complained that severe paroxysms of pain developed following the removal of an unerupted and apparently impacted lower right third molar. This tooth had been extracted for prophylactic measures. The paroxysms of pain were intermittent in character and there was an area of tenderness posterior to the ear on the affected side. Roentgen examination revealed what appeared to be a retained root in contact with the mandibular canal. No particular rarefaction involved the former. Following a second operation for the removal of the root apex, there has been no further discomfort.

Case 5: The patient was a child 15 years of age who complained of persistent headache. The anterior deciduous teeth had been lost as the result of an automobile accident at the age of three years. Examination of the lateral teeth showed marked hyperplasia of the enamel, incomplete formation of the root canals and the response to the vitality test was weak. A diagnosis of bilateral radicular cystic formation of the maxilla, apparently originating from the lateral teeth, was made, and following complete enucleation of the cystic membranes, the headaches disappeared completely.

Case 6: This patient had a severe pain in the pterygomandibular region and suspected that a tooth might be the cause. A radiographic negative devitalized bicuspid tooth with the root canal well filled was revealed. Removal was deferred at that time, but extraction was advised if the pain persisted and no other positive findings were discovered. The following day, while the patient was in the hospital and his temperature ranged from 100° to 103°F., a definite bulging of the mucosa appeared in the retromolar area, almost obscuring the third molar. This had not been observable the previous day. The condition rapidly became worse and the patient expired four days later. The diagnosis of cavernous sinus thrombosis was established at autopsy, and the probable etiologic organism was a Staphylococcus albus. This organism was also found on culturing the devitalized tooth which was removed at autopsy.

This case is mentioned because symptoms referable to the teeth were marked early in the course of the disease but they were not the primary cause. Removal of the tooth undoubtedly would have been followed by the inevitable sequence and possibly would have carried out the resultant censure.

In regard to the temporomandibular disarticulations with pain which Goodfriend[4] describes as dysarthrosis, subarthrosis, and subluxation, the essential value of maintained normal occlusion is emphasized, and strong arguments are advanced for the replacement of the missing teeth in order that the masticating function may be maintained and loss of vertical dimension prevented. Costen[5] reported the cases of 125 patients who had headache and symptoms referable to the ear. He states that improvement followed restoration of the normal occlusional planes in functional activity and correction of the vertical relationship, thus bringing the temporomandibular articulations within the normal range.

Another factor to be considered in determining the etiology of neu-

ralgia is described by Mead[6] as primary chronic osteomyelitis. "The process of primary chronic osteomyelitis is an insidious one, and the symptoms are often vague and indefinite. In fact, the symptoms may be so slight and so ill-defined that the patient is not aware that any disease is present. It is therefore a chronic inflammatory process of long standing. The objective symptoms are occasionally a bulging or swelling of the buccal or lingual plate or in some rare cases there is an escape of pus or purulent matter from a small fistula in the mouth. The subjective symptoms are usually the diagnostic factor in bringing to the operator's attention the presence of this type of disease. The patient may complain of an indefinite or ill-defined pain radiating back of the ear, above or below the eye, or complain of a dull, heavy, uneasy sensation of the particular region involved." I have not been able to demonstrate this type clinically, but such a condition has been suspected in two cases of broken-down septic areas.

Pain may also be associated with a galvanic current, the marked electrical flow between dissimilar metals in a saline or acid media. This subject has been investigated by Lain[7] who has used a small galvanometer to measure the flow between restorations composed of different metals occupying a wide position in the electromotive series range. He has estimated that about 33.7 per cent of the patients examined exhibited mild electric shock. This simulates a pulpitis and is often referred to other teeth.

In the injection of novocaine into the tissues for local anesthesia, the tonicity of the solution may be a factor in facial neuralgias, particularly in nerve block injections where the solution is placed in close proximity to, or involves, one of the divisions of the fifth nerve. With the use of hypotonic solution, a process of endosmosis results in which the solution diffused into the cells will cause a ballooning and possible bursting of those cells. A hypertonic solution, on the other hand, produces an exosmosis, with resultant shrinkage and death of the cells. Either solution may conceivably be the cause of a sclerosis of nerve tissue or adjacent tissue with possible pain reflex.

In conclusion, it should be emphasized that a complete oral examination as well as a physical examination is necessary to rule out all possible causes of neuralgia. The roentgen examination is not sufficient, and an investigation should be made from the standpoint of occlusion of teeth, restorative measures, and a complete history in regard to the time, method, and reason for the extraction of any missing teeth. In

the diagnosis and treatment of such conditions, the closest cooperation must exist between the medical and dental professions.

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THE SURGICAL TREATMENT OF DIVERTICULITIS

THOMAS E. JONES, M.D.

The surgical problems presented in the treatment of diverticulitis do not parallel those of acute appendicitis in many cases. However, the differing opinions held by men of wide experience cannot be dismissed without serious thought.

Erdmann in 1932 reported a series of 71 cases of diverticulitis and stated that the acute condition of the abdomen presents but one solution to him and that is early operation. He believes that one should no more wait for resolution in an abdomen in the acute type of this disease than in an allied condition due to appendicitis or to suppurating tubes. However, he does not state the specific type of treatment in a given number of cases, and he does not state the mortality from the various procedures so that it is difficult to make a comparison with other series.

In reading case reports in the literature, one is impressed by the number in which exploratory operation was done during the acute phase of the disease with termination a few days later in death due to peritonitis. One is justified in wondering whether or not localization might have occurred in a certain percentage of these cases in a period of days and surgical intervention later might have been more safe. This condition calls for more individualization than does acute appendicitis, and while general rules may be formulated, each patient must be studied carefully.

One outstanding clinical fact is that diverticulitis is practically always confined to the sigmoid colon, even though the diverticula may be very extensive and involve the entire colon. There are few reported cases of complications developing in diverticula in other segments of the colon. This is probably due to the smaller caliber of the bowel and the firmer stool in the sigmoid area.

The symptoms vary greatly according to the pathologic condition found. There may be only mild attacks of pain in the left lower quadrant and any graduation up to the signs and symptoms arising from grave complications such as perforation with peritonitis, obstruction, or formation of a fistula.

An accurate history is invaluable, and a careful differential diagnosis must be made in some instances. Any given case in which operation is not performed will terminate in one of the following ways:

1. The diverticulitis may resolve completely but this, of course, does not militate against subsequent attacks either in the same diverticulum or in others in the same segment.

2. Perforation may occur:
   a. Into the rectum with discharge of pus
   b. Into the bladder
   c. Into the surrounding tissues and become walled off
   d. Into the surrounding tissues without becoming walled off but is generalized with resultant peritonitis.

3. Obstruction may result in cases where the process is not resolved. This is due to great thickening of the mesentery and all coats of the bowel.

The important problem then is, should operation be performed, and if so, when is the optimum time? This is most difficult to answer in the fulminating variety and here surgeons differ widely. The answer depends somewhat on when the surgeon saw the patient in relation to the onset of the attack. If seen early—within 12 hours—it may be justifiable to explore. If a long diverticulum without too much thickening of the bowel wall is found, excision and suture may give a brilliant result, but such cases are greatly in the minority.

In cases where there is considerable thickening around the diverticulum, a Mikulicz type of operation may be used. This may be done easily in a long movable segment of the bowel, but if the bowel must be mobilized to a considerable extent to bring it out, it is not a safe procedure in the presence of much infection. The other alternative would be to do a colostomy above the inflammation and place drains down to the affected area in order to form a channel should an abscess develop. In cases where the mesocolon is greatly thickened, it is well to incise the peritoneum of the mesosigmoid for the relief of tension and for drainage.

However, the diagnosis of this variety is not often thought of early and the surgeon generally does not see the patient until several days have elapsed. By this time, there is considerable distension and it is not a simple matter to decide the best procedure. Judging from the reported cases, the mortality rate is high and I personally wait for localization. If there is evidence of any obstruction whatever, an immediate cecostomy is performed, this being away from the infected area. Clinically, more of these localize than perforate into the general abdominal cavity, thus causing peritonitis. If they localize, they can be drained laterally.

In the subacute variety, no emergency exists and sufficient time may be taken to establish a more accurate diagnosis. Roentgen examination is of great assistance in determining the location of the diverticula and their extent, and in this way, a well planned operative procedure may be carried out. If the process is limited to one segment, involving perhaps four or five inches of the sigmoid, the area may be resected, and an end-to-end anastomosis made. The same principles apply to resection

here as they do for resection of a neoplasm; i.e., some type of preliminary decompression operation should be done before the resection, such as transverse colostomy or cecostomy. If the diverticula extend throughout the sigmoid and descending colon, however, one must resort to expectant treatment or perform a colostomy which may or may not be a permanent one.

When patients are observed who have had a subacute condition over a period of 10 or more years with occasional attacks which clear up, it is quite difficult to recommend colostomy in all cases. Many of these are physicians who certainly will not have a colostomy, but prefer to endure the occasional inconvenience. So, I do not think it is justifiable to force patients to have a colostomy as long as they understand that an attack may come along which makes operative intervention imperative. Furthermore, resection of one segment, when many more diverticula may be present above or below, does not insure the patient against further attacks in the remaining ones.

If the subacute variety goes on to tumefaction with tenderness and low grade fever—up to 101° F.—it will be well to treat the patient conservatively and wait for an optimum time to make a left McBurney incision and drain the abscess. Again the surgeon must determine the optimum time for this. Of course, a fistula often develops through which feces will drain at first, but later on this becomes a simple sinus which may close in a month or it may take six months to heal. It is of little inconvenience to the patient, and no attempt should be made to close it for at least a year, and then only on the insistence of the patient.

Roentgen examination of the sinus tract with bismuth will outline its location and if any operative intervention is planned, it will be best to prepare the patient for resection of the segment because excision of the sinus with inversion of that particular area of the bowel will fail in most cases.

Particularly distressing are those instances in which a fistula has occurred into the bladder. If the opening is not too large, colostomy alone will occasionally permit of its closing but, if it does not, the constant infection in the lower loop will keep up the infection in the bladder and necessitate its closure surgically. With a preliminary colostomy having been done, the bladder may be closed and the affected segment of the colon resected after whatever method seems best.

I have reviewed the 16 cases that have come under my observation in the five year period from 1930 to 1935. Six of these patients were seen in consultation and 10 were operated upon personally. I think a very brief review of these cases will serve to show that no single method of treatment is possible or feasible.

Case 1. (1931): A woman had had pain for two weeks and it had become severe in the two days preceding examination. The temperature was 100° F. A palpable mass was present. After drainage, healing occurred, and the patient has remained well.

Case 2. (1934): A man was operated upon three days after the onset of pain in the lower quadrant. A diagnosis was made of diverticulitis with symptoms of obstruction. Colostomy was performed and this was closed six months later. The patient has remained well.

Case 3. (1933): This patient, a man, was admitted to the hospital three days after the onset of his attack. The temperature was 102° F. A mass was palpable but there was no obstruction. Expectant treatment was instituted, the temperature continued to be elevated for seven days but subsided in ten days and no operation was performed. The patient has had no trouble for two years.

Case 4. (1932): For several days before admission, this man's temperature had been 102° F. A palpable mass was present and a diagnosis of diverticulitis with abscess was made. Operation was advised but the patient refused. When he returned to the hospital four days later, complete obstruction was present. Cecostomy was performed and dirty bloody fluid was found in the abdomen and there was definite peritonitis. Death occurred seven days after operation.

Case 5. (1930): The patient was a man who had multiple diverticula with abscess and fistula into the bladder. Colostomy and drainage of the abscess were performed and recovery was uneventful. The fistula into the bladder is closed but he still has the colostomy which is advisable on account of the extent of diverticulosis.

Case 6. (1930): A woman had diverticulitis without abscess. She had experienced a similar attack which subsided six months previously. Cecostomy was performed with resection of four inches of the involved area and end-to-end anastomosis. The patient has remained well.

Case 7. (1934): A man was referred with a diagnosis of obstruction due to cancer. Investigation proved this to be caused by diverticulitis. A colostomy was made and the abscess drained into the bowel. The colostomy was closed six months later when roentgen examination revealed a normal lumen.

Case 8. (1934): This patient, a woman, was also referred with a diagnosis of malignancy. Her chief symptom was of obstruction and investigation revealed it to be due to extensive diverticulosis with diverticulitis. Colostomy was made and she does not want it closed because she is comfortable and relieved of an old, long standing constipation.

Case 9. (1934): A man was operated upon elsewhere two years previously for drainage of an abscess of diverticulitis. A sinus persisted and the abscess had recurred twice. A cecostomy was performed with resection of five inches of the sigmoid and end-to-end anastomosis. The patient recovered.

Case 10. (1934): This man had diverticulitis with abscess and obstruction. Cecostomy was performed. Localization of the abscess was apparent in one week and this was drained through a left McBurney incision. The sinus persisted for eight months but closed spontaneously and the patient has been well for more than a year.

The mortality in this series was 10 per cent.

It is obvious that each case presents a problem of its own and that a certain amount of experience with acute conditions of the abdomen is necessary for good surgical judgment in the handling of these cases.

Conclusions

The surgical treatment of diverticulitis is the management of the complications which may arise from a diverticulum and those complications are perforation, obstruction and formation of a fistula.

EFFECTS OF LIGHT, SUN, AND OTHER RAYS ON GROWTH*

OTTO GLASSER, PH.D.

(Assisted by Margaret Schott)

Glasser: For thousands of years the sun with its light and heat has commanded the attention and worship of mankind. Primitive man knew that there are great healing powers in the mighty rays of the sun. In the early civilizations the sun-god, Ra, of the ancient Egyptians, and Apollo, of the Greeks and Romans, was acknowledged to be one of the principal deities. The mythological beliefs which ascribed to the sun-god power over vegetation, growth and development, healing of sickness, life and death, have been well substantiated by modern science. Indeed, the ancients were conservative in their viewpoint. They might have been astounded could they have foreseen the almost fantastic discoveries of recent years.

Although it is an everyday experience to observe the importance of the sun's radiation to living things, I imagine that few of us suspect how closely our lives are linked with sunshine. On an overcast summer day, when the world seems unusually quiet, what wonders a sudden burst of sunshine will do to Nature, producing life and activity everywhere. As we shall see, everything in man's life depends upon the sun.

Perhaps the most fascinating mystery of the universe is the origin of physical life upon the earth. Protoplasm, the stuff out of which our bodies and those of every living thing are made, contains water, carbon, nitrogen, and other chemical elements. Although we do not know what vital spark transformed these lifeless chemicals into the first protoplasm, it is highly improbable that this mysterious and important substance could ever have been formed, not to mention being maintained, without the aid of light and heat. For we know that the sun's radiation provides energy for the conversion of inanimate matter into the complex machinery of the living organism.

Our interest is not confined to the sun's radiations, however, for these are actually only a small part of the different types of rays which are known to us, or, as the scientist may say, a small part of the total spectrum of electromagnetic waves. Now, may I ask before I go on, whether you are familiar with the term "spectrum," and with the term "electromagnetic wave," Miss Schott?

*This discussion was delivered on January 27, 1937 over the Blue Network of the National Broadcasting Company. It was the fifteenth lecture of the "Radio Forum on Growth and Development of the Child," under the joint auspices of the National Congress of Parents and Teachers, the American Academy of Pediatrics, and the National Broadcasting Company. (Editor of the Forum: Norman C. Wetzel, M.D., Cleveland, Ohio.)

Schott: Well, yes and no, but I should appreciate your explaining what you mean by the phrase spectrum of electromagnetic waves.

Glasser: That is not at all a difficult matter, Miss Schott, if you will recall that x-rays, ultraviolet light, and radio waves are all quite similar to the rays of ordinary sunlight, and travel through space at the same enormously high speed as sunlight—indeed so fast, as you know, that they will pass almost eight times around the earth in one second! Now, some radiations can be seen by the eye, whereas others cannot. Take this diagram, for example, which represents the entire electromagnetic spectrum we are talking about, and you will see that the word spectrum merely refers to the whole set or band of these radiations, some visible, and others, in fact many more, not visible at all.

Schott: Why, yes, here in the center of the diagram are the seven colors of the rainbow! Red, orange, yellow, green, blue, indigo, and violet! They are all here.

Glasser: And those seven colors are the only radiations the human eye can see. You see them in the rainbow, on the surface of an oil puddle in the pavement, or when light strikes highly polished cut glass.

Schott: Oh, certainly! You know, one of my favorite sports as a small child was blowing soap bubbles and admiring their mysterious colorations. Are these iridescent reflections of light related to the visible spectrum?

Glasser: Yes, they are. The white light that comes from the sun is actually composed of the seven colors you see in the center of this diagram. Sunlight is broken up into its component hues by the droplets of water in the clouds, in the films of oil, in the glass prisms, and in your soap bubble.

Schott: Then the rainbow with its series of seven different colors constitutes the visible part of the whole spectrum?

Glasser: Exactly. The rainbow, as this diagram shows, is only a small part of the entire electromagnetic spectrum. The invisible spectrum, containing the rays our eyes cannot see, is really very much greater than the visible part, and extends on the diagram, on either side of the visible rainbow part in the center. That is, some radiations have a longer wavelength, some have a shorter wavelength, than visible light.

Schott: Just what do you mean by wavelength?

Glasser: Have you ever thrown a stone into the water and watched the little waves move away in all directions? The distance from the peak of one wave to the peak of the next wave is what we call the wavelength. All electromagnetic waves, such as light, travel through space in much the same fashion that waves pass over the water; in some types

of radiation the distance between waves is short, in others long; hence, we measure different kinds of radiation by their wavelengths.

Schott: Is this what we mean when we speak of ether waves in connection with radio communication, and of Station WGAR, one of the many stations in the Blue Network over which we are now speaking, as operating on a wavelength of 206 meters?

Glasser: Yes, Miss Schott. The wavelengths used in broadcasting are millions of times as long as those of visible light, and as you know we cannot see them striking the aerial wires of our radio sets.

Schott: Now, I understand, but there are two invisible parts represented in the diagram here, one on either side of the rainbow. Which of these contains the radio waves?

Glasser: Since the radio waves are longer than red light, they appear in the diagram farther and farther out to the right as they become longer. As we get in closer to the red we meet the infra-red waves which produce heat; you can feel them, but you cannot see them when you stand before a heated oven or furnace.

Schott: Don't you also feel them in front of an open fireplace?

Glasser: Yes, of course.

Schott: Ah, but you just told us they are invisible.

Glasser: Those rays you see in the glow of the burning embers are not the infra-red or heat rays, but rather the actual red rays; the heat rays which you cannot see, but which you feel as warmth, are simply produced by the fire at the same time.

Schott: That's quite clear now. What about this other invisible part of the spectrum extending to the left of the violet and blue end of the rainbow? Would these rays then be the cold rays?

Glasser: Those nearest and to the left of the visible violet are the invisible ultraviolet rays. They could be called cold rays only in the sense that the heat they produce is too small to be detected except with sensitive laboratory instruments. But they do have very pronounced chemical and biological effects.

Schott: Are they the rays which tan the skin?

Glasser: Yes, they are. Farther out to the left of them, with continuously decreasing wavelength, you find the x-rays, and beyond them the gamma rays.

Schott: I think I know something about x-rays but I'm not so sure about the gamma rays.

Glasser: Gamma rays come from radium. They are one of the three kinds of rays which are continuously generated by the explosion of the tiny radium atoms; they are so powerful that they can penetrate steel bars several inches thick.

Schott: They must be similar to x-rays, then.

Glasser: Yes, they are. On the other hand they are also similar to the cosmic rays, the last group here at the left, the very shortest waves we know today.

Schott: Are these the cosmic rays of which we read in the papers, especially in connection with stratosphere balloon flights?

Glasser: Yes, Miss Schott. The cosmic rays, as the name implies, arise in the starry spaces of the heavens and, for many reasons, are the subject of a great deal of scientific investigation today, but primarily perhaps because the earth and its people are being continuously bombarded by them.

Schott: Well then, Dr. Glasser, you have now described all the different electromagnetic radiations we know today. These range, as I can see from this diagram, from the shortest invisible cosmic waves here on the left, up through the continuously longer gamma rays, x-rays and ultraviolet rays, to the visible spectrum with its rainbow colors. Then, beyond to the right, the much longer infra-red heat waves, ending with the longest of all, the electrical radio waves. Do all these originate in the sun?

Glasser: No, indeed. The earth receives from the sun and diffuse skylight only heat, light, and ultraviolet waves. But man has succeeded in imitating the sun by producing heat and light artificially with oil lamps, torches, candles, and in recent years with electric lamps. Man has also learned how to produce ultraviolet rays by means of special kinds of lamps. But beyond that, man has even produced rays that are not contained in sunlight, such as x-rays, and radio waves.

Schott: This is interesting, but do all these radiations play an important rôle in our lives, especially with reference to growth?

Glasser: Most, if not all, of these radiations are of fundamental significance in our lives, our development, and our growth. Indeed, as I mentioned previously, it is certain that we owe our very existence to the heat and light of the sun, for these make our climates favorable to the continuation of all plant and animal life.

Schott: But I thought, from what Drs. McCollum and Weech told us a few weeks ago, that our energy was derived primarily from the sugars, starches, fats, and proteins in the food we consume.

Glasser: The immediate source of our energy is, as you say, food. But that energy was originally stored in green plants and vegetables, which themselves received part of their energy from the sun. As you know, spinach, lettuce, and other green leaves are little factories which take raw materials from the soil and from the air and manufacture the complex substances used as food for animals and men. But

this happens only when the plants are properly exposed to the sun. The method by which plants can store food energy is something that man has as yet been unable to imitate, and therein lies one of the most important questions confronting modern science. Consider, for example, what the use of wood for fires, in building homes, the use of coal and petroleum deposits as fuel, of cotton for clothing, the cheap manufacture of paper, have meant in the marvelous unfolding of civilization as well as in the development of the race, and that all these can be traced to sunlight.

Schott: In spite of our pride in human achievement, it seems that we are dependent ultimately on the sun's radiation not only for our nourishment, but for clothing, shelter, fuel—all the things which make progress possible. Now, if sunlight is not available, does plant growth cease altogether or can some other source of energy be utilized?

Glasser: With all our ingenuity we shall never be able entirely to do without the sun. It is possible, however, to supplement the sun with other kinds of energy. In recent years it has been found that when the supply of sunlight is insufficient, as in greenhouses in the winter, artificial light can be used as an excellent substitute for sunlight. Tomato seedlings, for instance, can be speeded up in growth before outdoor planting. Curiously enough, the different portions of the sun-spectrum are not of equal value to the plant. The green coloring matter contained in the leaves does not take up all the light it receives; it takes up only certain kinds of light, for instance, red-orange may be used for building up sugars and starches, while shorter rays in the violet range are needed to form proteins. Some radiations are actually injurious and could, if properly employed, eliminate weeds and plant parasites, thus aiding desired plant growth.

Schott: Do I understand correctly that the biological effect of any kind of light is merely a matter of its color—that is, of its wavelength?

Glasser: It is necessary to keep in mind the distinction between quality—that is, the wavelength—and quantity of radiation. It is a general rule that those wavelengths which are needed have to be absorbed in order that their energy may be utilized. The green leaf retains the red-orange light which stimulates growth and chemical processes while permitting the useless rays to pass through. An insufficient amount of radiation of any wavelength will be ineffective. On the other hand, too much of a beneficial radiation can do a great deal of harm. I do not need to tell you that although a moderate amount of ultraviolet light is healthful, too much exposure results in painful and sometimes serious consequences.

Schott: Is sun-bathing actually as beneficial as many of us believe, especially for children?

Glasser: All the benefits to be derived from sunlight are not yet known. It is, however, well known that ultraviolet light is essential to healthy development because it stimulates the formation of the sunshine vitamin D, which prevents rickets and helps to regulate not only the growth of bones and teeth, but the growth of the entire body as well. Ultraviolet light acts by producing a chemical change in the substance, ergosterol, converting it into vitamin D, which, as you know, in exceedingly small quantity is equivalent in its effectiveness to enormous doses, even quarts, of cod liver oil.

Schott: Does the ultraviolet light penetrate deeply into the body in order to produce its effect on bones and teeth?

Glasser: No, ultraviolet light and visible light are absorbed at the surface by the skin. It is here that the production of vitamin D from ergosterol contained in the glands of the skin occurs. But it has been observed that ultraviolet light absorbed in the skin has also an effect upon deeper seated organs; for example, in healing certain forms of tuberculosis. There are other close connections between ultraviolet light and growth. You are familiar, for instance, with the fact that certain animals can give off visible light?

Schott: You mean the fireflies and the tiny animals which produce the phosphorescence of sea-water when you disturb them?

Glasser: Exactly. Now, whereas all animals give off heat as a by-product of their activity, some give out light in addition. It is not startling therefore, to learn that scientists today are investigating the possibility that ultraviolet light might be produced by the work of body cells. This radiation may in turn stimulate other cells to reproduce themselves, thus aiding or hastening the process of growth.

Schott: But has such a radiation actually been observed?

Glasser: With sensitive devices, such as those used for capturing cosmic rays, it has been claimed that an ultraviolet radiation can be observed from active muscles, for example. In time, as the methods are improved, it may be possible to detect a difference in radiation between healthy and diseased tissues or bodies. The widespread usefulness of such a method to medical science can be easily imagined, but it has not, as yet, passed beyond the stage of laboratory experimentation.

Schott: From what you have said, I should conclude that sunlight is essential as the source of energy required for vital processes, and that ultraviolet light is extremely important in determining healthy growth. Are there other forms of radiation which are beneficial?

Glasser: Thus far I have told you only of the obviously beneficial effects, but there are other short wave radiations which, although harm-

ful, can be used to promote normal growth. This seemingly paradoxical action is found in x-rays and the gamma rays of radium. The effect which these radiations have in depressing growth and even destroying tissues provides the physician with a powerful method for controlling unwanted or abnormal growths or other factors which may suppress growth, thus permitting the normal growth processes to continue unhindered. Of course, it is necessary to exercise great caution in administering x-rays and radium in order to protect the healthy tissues.

Schott: Are any of these radiations injurious enough to kill—in other words, death rays?

Glasser: Yes, indeed. X-rays and gamma rays will prevent the fertilized eggs of insects, such as the common fruit fly, from hatching. In high doses these rays may cause the death of an animal. Oscillations just shorter in wavelength than those used in broadcasting produce sufficient heat to kill small animals. Short ultraviolet has been shown to destroy bacteria and other harmful microbes. At the present time there is little likelihood that death rays can be projected far enough to be used as a weapon against anything as large as man. On the contrary, when judiciously applied, they can be used to our advantage. The heating effect of short wave oscillations is useful in combating certain diseases by inducing artificial fever in the patient. The killing action of short ultraviolet rays can be used in many ways; for example, to sterilize water for drinking purposes or in indoor swimming pools; in hospital operating rooms, or by the dentist to prevent infection and to promote healing of wounds; and commercially, to protect foods against mold formation.

Schott: Then even the death rays can be employed as aids to healthy growth. Are there any other ways besides those of which we have already spoken in which radiations, the powerful x-rays or gamma rays, for example, affect growth processes?

Glasser: Your question leads us to a highly interesting effect which x-rays and gamma rays have upon the development of the embryo. Several weeks ago Dr. Hersh spoke of the mechanism of inheritance, of the action of genes, those minute bead-like objects contained in the cells of the body, which we inherit from our parents.

Schott: By genes you refer to the immeasurably small units which determine, for example, whether or not a baby is to have brown eyes?

Glasser: That is correct. Any given gene, as he pointed out, always possesses the same properties, so that the only uncertainty in heredity is caused by not knowing how the genes will be shuffled, and what combination will appear in the fertilized egg. Once the genes have been finally sorted, the end-result, if development be left to itself, has been unalterably determined. It is possible, however, to cause a change in

the structure or composition of a gene with the x-ray, so that subsequently its effect upon development will not be the same. For example, in the common fruit fly, the offspring may have white instead of red eyes, or forked bristles in place of ordinary ones. Even ultraviolet light has been found to have similar action in altering leaf or flower arrangement in the snapdragon.

Schott: In other words, it is possible artificially to imitate Nature's process of evolution?

Glasser: Only in a limited sense. The long, slow process of evolution is undoubtedly not as simple as that. The chief radiations of short wavelength to which organisms are subjected in Nature are the cosmic rays. Now, although the number of cosmic rays which strike the body are few, the shower of cosmic radiation from the heavens is continuous, so that it is not impossible that in the course of years they might exert some effect. Indeed, it has recently been shown in experiments in which fungi were grown under lead shields of different thicknesses that the secondary radiations produced in the lead by the cosmic shower brought about changes in developmental growth pattern.

Schott: Since the various types of radiation have such important effects upon the welfare of an organism, is there any provision made by Nature to enable the organism to respond to radiations according to their desirability or harmfulness?

Glasser: Yes, there is such a mechanism. If you have ever gone fishing, you may have spent the evening before in capturing live earthworms with the aid of a flashlight. Worms and many other kinds of animals respond positively or negatively to light, that is, they move into it, or away from it. It is unnecessary to tell you that insects are attracted by light. It is possible to set up traps for insect pests in the garden and entice them into the traps at night with a lighted lamp.

Schott: I never before imagined that light and other radiations could have such a profound influence on our lives, or be put to so many uses. Would you be good enough, Dr. Glasser, to summarize briefly the important features of all you have told us?

Glasser: There are really four main effects which radiations have on growth and development. First, the stimulative effect of sunlight and heat upon plant life, because this provides the energy for the complex biochemical manufacture of food. Second, the beneficial effect of ultraviolet light in preventing rickets and regulating bone, tooth, and body growth. Third, the indirect benefits to normal, healthy growth derived from the action of x-rays, gamma rays, and death rays in destroying unhealthy growths and invading bacteria and microorganisms. Last, the alteration of inherited characteristics among certain organisms by the action of x-rays and gamma rays on their genes.

MANAGEMENT OF CHRONIC PEPTIC ULCER*

JOHN TUCKER, M. D.

In recent years, a large number of articles dealing with the subject of chronic peptic ulcer have appeared in the literature. Many writers have considered chiefly the problem of etiology, while others have advocated new and unusual forms of therapy. In an effort to sift the wheat from the chaff, we have found it necessary to direct our thoughts to the fundamental principles of the physiology of the gastro-intestinal tract. It seems to us quite evident that major symptoms of this disease result from abnormal disturbances in motility and secretion. The effects of local inflammation within the stomach or at the site of the ulcer appear to be secondary factors. In this discussion the various conceptions of etiology will be discussed and the principles of treatment will be considered. First, however, some general observations will be made.

Chronic peptic ulcer does not occur in the lower animals; it distinctly appears to be a disease of civilized man. As a cause of chronic indigestion, it surpasses in frequency all other abnormal states with the exception of chronic disease of the gallbladder. However, during the period of man's greatest mental and nervous activity—between the ages of twenty-five and fifty—it has no close rival. Among those patients who come to us complaining of chronic recurring indigestion and in whom we are able to make the diagnosis of a gastric or duodenal ulcer, there appears to be a definite constitutional type. This apparent predisposition is not related to the physical appearance of the body, whether it be tall or short, thin or obese, but rather to the nervous makeup of the individual. The gastric or duodenal lesion is discovered in the asthenic or sthenic patient with nearly equal frequency, yet many clinicians would have us believe that the mere physical conformation of the body is of considerable significance. This has not been our experience because we have found that the energetic executive or professional man is the favored host, be he large or small, thin or fat. Like hyperthyroidism and diabetes, this disease attacks those individuals who take the responsibilities of life too seriously. Peptic or duodenal ulcers rarely affect the phlegmatic races, such as the Slavs, Chinese or full-blooded Negroes. Among the mulattoes who have an admixture of the white and black blood, ulcer occurs more frequently than in the pure blooded Negro. Recently, we were consulted by the President of a University for Negroes. This patient, while partially

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black, was suffering from a duodenal ulcer and he was a nervous but highly intelligent man.

Before the therapy of chronic peptic ulcer is discussed, it is quite necessary that the various known facts which serve to explain the clinical picture of this disease be understood. These theories can be grouped into three general headings, the neurogenic, vascular and acid erosion theories.

I. Neurogenic Theory

Rokitansky was probably the first physician to suggest that ulcerative lesions in the gastro-intestinal tract might have a neurogenic origin; on the other hand, Virchow regarded chronic peptic ulcer as a purely local process. Recently, the neurogenic conception has received strong support by the experimental and clinical observations of Dr. Harvey Cushing[1]. He observed that, in some instances, ulcers in the esophagus, stomach or small bowel have developed in patients who were afflicted with lesions of the interbrain, whether the central lesions were due to tumor growth or to inflammation. Even though these ulcers of probable neurogenic etiology have been acute in type and have failed to manifest all the characteristics of the chronic peptic ulcer, this may be due to the fact that the patients did not survive long enough for a characteristic chronic ulcer to develop. In his experimental work on animals, Cushing has presented much evidence to show that a parasympathetic center lies in the tuberal region of the diencephalon or midbrain. He has conceived the idea that the prolonged stimulation of such centers may produce ulceration of the gastro-intestinal tract. Even though these observations are not entirely conclusive, our clinical experience permits us to apply this theory to the genesis of peptic ulcer in man. Such an hypothesis would explain why local ischemia could occur in the gastric or duodenal mucosa by arteriolar or smooth muscle spasm, the stimuli passing from the midbrain along the vagus nerves. It would explain how gastro-intestinal hypermotility and hypersecretion might occur from the effects of a prolonged period of fear, apprehension or anxiety, the results of the wear and tear of modern civilization. Great enthusiasm for this theory may not be fully warranted in the light of experimental work but, on the other hand, it meets the experience of clinical practice.

To summarize the important features of the neurogenic theory, the following observations may be made:

1. High strung people are particularly susceptible to nervous indigestion and ulcer. The tendency to ulcer is in direct proportion to the duration and severity of the nervous strain. It is especially during the episodes of excessive worry that the ulcer first appears or a recurrence of the old ulcer takes place.

2. Ulcers tend to heal when the patient is put at mental and physical rest. A prolonged ocean trip or a month of rest at a resort, among pleasant surroundings and where simple diversions are available, may accomplish better and quicker results than medical care at home.

3. When the patient returns to his former environment and if the emotional strain is not lightened, the symptoms of ulcer tend to recur.

It is quite true that important agents other than excessive nervous strain lead to formation of an ulcer. These are included in the vascular and acid erosion theories. Some significance may also be attached to the influence of dietary indiscretions, the excessive use of tobacco and alcohol, the influence of allergy, and various disturbances in the endocrine glands. In most instances, it would appear that these factors, if present, affect and mediate through a disturbance in the vagal or, in some instances, the sympathetic control of the function of the gastrointestinal tract.

II. Vascular Theory

If the blood supply to any area of the gastric mucosa is diminished beyond the critical level, there will be a loss of vitality and finally ischemic necrosis takes place. Such an interference with an adequate circulation may be brought about by arteriolar or capillary spasm, by obstruction with sterile or infected emboli, by local endarteritis accompanied by thrombosis or by intramural hemorrhage. This devitalized area in the mucosa is then digested by the combined action of the acid gastric juice and pepsin. This concept is strengthened by the fact that microscopic examination of pathologic sections of chronic peptic ulcer fairly frequently show obliteration of the arterioles by endarteritis and thrombi or by emboli. Hauser[2] and Eggers[3] believe that localized hemorrhage causes death of the tissue at the site of an obstructed vascular supply and that ulceration of the mucosa soon follows. On the other hand, many observers attribute such changes to the secondary effects of ulceration and maintain that this reaction is not a primary agent. Be this as it may, there is considerable histologic evidence to show that the arterial blood supply to the ulcer-bearing areas of the stomach and duodenum are not very plentiful and that minor vascular accidents may seriously impair the nutrition of the tissue in these regions. Postmortem studies show that, in many instances of chronic ulcer, the nutritional disturbances begin well below the gastric and duodenal mucosa. Robinson[4] has found that, in the typical peptic ulcer, greater damage is manifested in the submucosa and muscularis and that, at the onset of the lesion, the least damage is seen at the mucosal surface. In other words, the vascular obstruction with secondary necrosis begins well below the mucous membrane. As a result, according to Morton[5], the crater of the ulcer is often cone-shaped with the apex

toward the mucosal surface and the base resting on or within the muscularis. Furthermore, many specimens show that the healing of the ulcer progresses more rapidly in the mucosa than in the submucosa. Conversely, if the ulcer were due to acid erosion and nothing else, the most extensive portion of the ulcer would be at the mucosal surface with the lesser damage in the bowel wall.

If these observations be correct, we have some evidence to show that the primary devitalization is due to an interference with the local vascular supply in the deeper layers in the wall of the stomach and duodenum. This concept would lead us to conclude that the acid-pepsin erosion is of secondary importance. Autodigestion would serve merely to remove the tissue which has been devitalized by local ischemia.

As a further elaboration of the theory that a chronic peptic ulcer is produced by an interference with the local blood supply, several investigators have attempted to show that this is brought about by bacterial emboli. E. C. Rosenow[6] of the Mayo Clinic has been the principal exponent of this idea. His method has been to make cultures from infected teeth or tonsils of patients with ulcers. Such bacteria were grown on culture media of suitable oxygen tension. When suspensions of these bacteria were injected into the blood streams of laboratory animals, he has observed ulcers in the stomach or duodenum at postmortem examination. He has expressed this reaction as the "specific elective localization of bacteria." With the use of this same technic, some investigators have been able to verify these observations while others failed to corroborate his findings. From a clinical standpoint, we have no way of knowing whether we have prevented or cured peptic ulcers by the removal of foci of infection. After the ulcer has become established in a patient, the good results which may follow the removal of septic foci could very well be due to the accompanying dietary and medical management or to a natural remission of the disease. The late Lord Moynihan expressed the belief that, in some cases, a chronic peptic ulcer apparently heals after the removal of an infected appendix. We believe that we have observed this effect in an occasional case. On the other hand, the relief of digestive symptoms can be explained again by the effect of the general and detailed care of the patient.

III. Acid Erosion Theory

In the acute, painful stage of peptic ulcer, excessive quantities of hydrochloric acid are usually found in the stomach. A true gastric or duodenal ulcer does not develop in the presence of gastric achlorhydria. Both hydrochloric acid and pepsin are required to produce the ulcer. These are aphorisms which warrant little dispute. With few excep-

tions, authorities agree on these points—*no acid, no ulcer—plenty of acid, possible ulcer.* Many facts furnish support to this concept:

1. The pain of peptic ulcer is relieved by substances which neutralize or combine with hydrochloric acid. These consist of alkalies, proteins, mucin, and hydroxides of metals such as aluminum.

2. The pain is often controlled by a high fat diet which serves to inhibit the secretion of acid. Among these are the fats of meats and vegetables, cream and olive oil.

3. Peptic ulcer may develop in regions not ordinarily exposed to hydrochloric acid, such as in the mucosa of the terminal esophagus or in the jejunum after gastro-enterostomy. Likewise, at times a typical peptic ulcer may appear in a Meckel's diverticulum when aberrant gastric tissue is present in this structure. It would appear reasonable to venture the opinion that simple erosion can occur in those regions not accustomed to the presence of acid, without the need of any preliminary interference with the mucosal blood supply.

4. A peptic ulcer may heal when bathed by a high concentration of hydrochloric acid if the denuded area is protected from the erosive effect by some inert substance such as a large quantity of bismuth, aluminum hydroxide or mucin.

These points give considerable strength to the premise that acid and pepsin are necessary for the formation of an ulcer. However, under ordinary conditions, when the mucosa is in a healthy condition, the stomach and duodenum can maintain the integrity of the living mucous membranes. Autodigestion does not take place in normal tissue. For example, a glassful of beef blood can be swallowed and digested without difficulty. This acts as a food. On the other hand, any of our own blood that may be extravasated into the stomach by a bleeding ulcer or which may be swallowed during nose bleed or after a tonsillectomy will not be digested or utilized by the body. It is either vomited or passed by the bowel as a black, tarry, foul mixture. Vital tissues of the body are not destroyed by the normal enzymes.

The gastro-intestinal hypermotility and hypersecretion which occur in the ulcer state have important therapeutic significance. By roentgen studies one can demonstrate either hyperperistalsis in the stomach and small bowel or in many instances a definite pylorospasm. When the gastric contents are evacuated by means of an indwelling gastric tube, it can be shown that there is hypersecretion of a highly acid chyme. It is generally recognized that this irritable state in the muscles and glandular tissues of the digestive tract is due to autonomic imbalance, commonly termed vagotonia. The state of pylorospasm has been termed "pyloric achalasia" by Hurst[7], the eminent English clinician. This

condition of functional pyloric obstruction interferes with the normal regurgitation of alkaline duodenal fluid into the stomach. The gastric secretion remains highly acid. Healing of an ulcer is delayed unless means are taken to relax the pylorus. On the other hand, the alkaline "buffer" effect of the duodenal secretion may be lowered by associated biliary or pancreatic disease.

Other theories of the genesis of peptic ulcer will not be discussed here. Studies in the fields of allergy and endocrinology are as yet too incomplete for the findings to be utilized in any therapeutic program. Clinicians are interested only in the practical application of all facts and theories which may be used as guides to rational treatment. Furthermore, not only the immediate relief of the ulcer symptoms must be considered, but the *prevention of the cyclic recurrence of this disease* is of importance also. After a careful survey of the known facts and theories and in the light of our own experience with chronic peptic ulcer, we are quite convinced that the nervous factor is of primary importance and that all other influences are secondary to the autonomic imbalance. Our patient is a civilized being, he is beset by the responsibilities of his work and his home. Modern competitive business affects people in all walks of life. Hyperemotional states and nervous fatigue are a common misfortune. These excessive stimuli disturb the normal physiology of the stomach. The reactions are somatic. Day after day there is pylorospasm, gastro-intestinal hypermotility, gastric hypersecretion, and also probably spasm in the peripheral arterioles and capillaries, both on the body surface and within the viscera. We have no simple explanation of these phenomena—they are civilized man's reactions to his environment.

Treatment

The treatment of peptic ulcer requires a definite plan of education. Like the care of such diseases as diabetes, tuberculosis, syphilis or chronic heart disease, the full and intelligent cooperation of the patient must be gained if treatment is to be successful. The patient must not throw the whole burden of his disease on the physician's shoulders but he must work intelligently *with* his medical advisor.

Habits of Living

At the best, we are never sure that a peptic ulcer is permanently healed. Relaxation in therapeutic vigilance will result in an exacerbation of the disease in most instances.

Our first and most important point in management is the modification in the patient's habits of living. He must secure tranquillity of mind and body as far as social and business conditions will permit. Nine hours of sleep at night, a midday rest of one-half hour, simple recreation

during leisure hours and, above all, a philosophical point of view are all vital and essential factors in therapy. A period of change away from the home environment is most valuable. In many instances, this cannot be managed, especially if the sufferer is a factory or office worker. However, his treatment can be individualized so that at least for a portion of the day he can secure an escape from reality. A short walk, moderate work in the garden, music, a hobby such as stamp collecting or carpentry can furnish a suitable avocation which will give a release from nervous tension. This treatment alone will not infrequently produce a remission of symptoms. A good fishing and hunting trip with companions who are not too convivial or, if circumstances permit, an ocean voyage will often hasten the subsidence of symptoms of ulcer.

Dietetic Management

The proper use of diet in the treatment of peptic ulcer has been the subject of controversy for many years. Some clinicians have continued to employ the Sippy diet, others the Lenhartz regimen. Likewise, diets outlined by Smithies, Coleman and Leube have been used with success. Such diets are rarely suitable to home treatment, because hospital care or the supervision of one trained in dietetics is required. In our experience, except in cases with gross hemorrhage from the ulcer, the patients do as well on a smooth diet as any other. With such food, there is little danger of any disturbing effect on the ulcer and, in addition, the diet is well balanced. The patient can eat tender meat, pureé of vegetables, day old bread, soft eggs, cereals, cooked fruits, milk and cream, simple pudding, and gelatin. As a rule, it is necessary to prohibit the use of tomatoes and fresh fruit until the acute symptoms of ulcer subside. The chief disadvantage of the Sippy and similar diets lies in the fact that they are deficient in iron and may be deficient in the essential, vital elements of food.

If the ulcer bleeds profusely, a preliminary starvation period of 24 hours may be followed by special diets. In several hundred cases, we have successfully used a smooth diet complemented by extra milk and cream midway between meals and at bedtime. Under this form of treatment the patients have been ambulatory and have been able to carry on their daily occupations with comfort, thus eliminating the customary period of two to four weeks in bed.

Medicinal Therapy

It is seldom that any unusual or complicated form of medicinal therapy is required. Despite some opinions to the contrary, belladonna or atropine are the most satisfactory antispasmodics. In all cases, unless there is an idiosyncracy to the drug, we give 12 to 15 drops of

tincture of belladonna before meals and at bedtime, four times a day. In a few instances, we have used sodium nitrate in doses of 1 grain. As a rule, the pylorospasm and gastro-intestinal hypermotility are definitely abated by the use of belladonna. The dose of this drug is easy to control.

We are employing alkalies in smaller and less frequent doses. A satisfactory prescription is one containing 2 parts of calcium carbonate and one part each of bismuth subnitrate and the heavy oxide of magnesia. At first, when the ulcer is very painful, this powder can be given in doses of one-half teaspoonful before meals, midway between meals, and at bedtime. Within a week, it is given only four times a day and soon two or three doses are sufficient in 24 hours. A few of my colleagues use colloidal aluminum hydroxide. This is given with the same frequency, two teaspoonfuls being taken at each dose, unless the patient does not tolerate alkalies well. Except in cases of severe nephritis, the alkaline powder is quite satisfactory. To my knowledge, we have not observed alkalosis when the dose of the powder was regulated in the manner described above.

The use of mucin is of distinct benefit. However, instead of prescribing the sticky, unpleasant commercial mucin, it is more satisfactory for the patient to produce and swallow that of his own manufacture. He is encouraged to chew gum with gusto. This procedure has the added advantage of affording some pleasure and of giving him something to do. It also acts as a substitute for candy and tobacco.

At times, in highly nervous patients, a bromide quiets the cerebral activity. During the first week of treatment, a prescription consisting of tincture of hyocyamus, 4 drachms, sodium bromide, 6 drachms, and simple elixir to make 4 ounces will not irritate the stomach if taken three times a day. Often it is palatable to take this mixture with the alkaline powder. As to the use of hypodermic preparations containing histidine, we are in accord with those authorities who believe that any apparent beneficial effects are largely psychological. At the present time, there are no short cuts in the treatment of chronic peptic ulcer.

General Measures

From the standpoint of general health, the patients must constantly be urged to live rationally and temperately. Adequate rest at night, a period of relaxation at midday, fresh air, sunshine, and moderate exercise all play an imporant part in the recovery. Definite foci of infection should be eliminated at the proper time. Disease in the pelvis or appendix may require surgical care. Simple hypochromic anemia will respond to adequate iron therapy but it is best not to give iron by mouth

until the painful stage of ulcer has passed. Such general measures serve to hasten healing and to prevent recurrence of the lesion.

The *ambulatory method of treatment of peptic ulcer* is employed in the majority of uncomplicated cases for the following reasons:

1. If the patient of limited financial resources is kept on the job, he has less anxiety about the welfare of his family. He cannot be expected to secure mental and physical relaxation if his limited savings are rapidly being exhausted.

2. His general strength will be preserved by keeping him on an adequate diet from the very beginning of his treatment.

3. He will be spared that difficult period of adjustment to normal living which often occurs after he has spent a few weeks in bed or in the hospital.

4. He will better realize that, while his disease is not of a critical nature, he must cooperate to the fullest extent by doing his share toward recovery. He is not being treated by nurses but by the advice of his physician.

5. The final and best reason is that this type of treatment, when intelligently carried out, works very well.

Under what circumstances, then, should the patient be sent to the hospital?

1. When he has suffered from one or more severe hemorrhages.

2. When roentgen examination shows that a penetrating ulcer or pyloric obstruction has not improved after due trial with ambulatory care.

3. When the physical condition is such that he must be put to bed and when the home care, under these circumstances, is inadequate.

4. When the home environment is uncongenial and when it interferes with proper mental and physical relaxation. Under such circumstances, if his funds are adequate, he will do better in a hospital or sanatorium.

5. If his pain is so severe that there is grave doubt as to the diagnosis or if there is the likelihood of perforation and peritonitis.

When these conditions exist, he can be sent to the hospital as a resistant case. While he is in the hospital, he can be given hourly feedings. Gastric intubation for the administration of aluminum hydroxide by continuous drip can be carried out under supervision. Of greatest

importance is the fact that he can be examined by a consulting surgeon who will be ready to open the abdomen should the ulcer perforate or symptoms of obstruction at the pylorus become acute.

Treatment of an Acutely Bleeding Ulcer

The patient should be put to bed at once. If there is vomiting of blood or melena, morphine sulphate, 1/6 grain, with atropine sulphate, 1/100 grain, should be given by hypodermic injection. He should be starved until bleeding has ceased for from 24 to 48 hours. An empty stomach is less likely to bleed. If bleeding will not cease, blood clots can be evacuated from the stomach by the careful use of a gastric tube. The lavage fluid may consist of four to six ounces of ice cold water and this lavage should be repeated until the water returns free of blood. If this is insufficient, the washing fluid may consist of 1:1000 solution of ferric chloride followed by the instillation of one drachm of 1:1000 solution epinephrine.

Blood transfusions are indicated if the hemoglobin falls to 40 or 50 per cent. Fluid is given by the intravenous route or by Murphy drip using 5 per cent glucose in physiological sodium chloride solution. A surgeon should always see the patient in consultation for, if these measures fail, operation will be required. Occasionally, in spite of all care and even though repeated transfusions have been used, the ulcer will continue to bleed and the patient will finally die. Hence, these cases constitute emergency problems and should be watched with great care and attention.

Indications for Surgical Intervention

The indications for surgical intervention in peptic ulcer are quite definite:

1. In cases of intractable ulcer.

2. In those cases of gastric ulcer in which biweekly follow-up roentgen studies fail to show regression of the deformity. All gastric ulcers are under suspicion of cancer until they show definite evidence of healing.

3. Pyloric obstruction which resists medical therapy.

4. Persistent or recurring massive gastric hemorrhage.

5. Acute or chronic perforating ulcers.

The following outline gives a general summary of the medical management of simple ulcers.

Rest in Bed	*Modification of Living Habits*		*Ambulatory treatment*
Diet	1. Dietary	Regularity	Diet
Lenhartz		Calmness	Smooth diet
Sippy		Vitamins	Extra cream
Smithies	2. Work	Tension at work	
Coleman		Dissatisfaction	
Leube		Worry	
Others	3. Social and Habits	Loss of sleep	
		Alcohol	
		Tobacco	
		Sex	
	4. Relaxation	Vacations	
		Midday rest	
		Hobbies	
	Medication		
	Olive oil		
	Alkalies		
	Atropine		
	Bromides		
	Mucin		
	Nitrites		
	Non-specific proteins		
	Removal of foci of infection		

Conclusions

We know of no criteria by which one can be certain that a patient is entirely cured of peptic ulcer. If his symptoms have abated and the roentgen evidence points to a normal contour and motility in the stomach and duodenum, we feel justified in regarding the disease as arrested. If the disease recurs, as it often does, it is due to the fact that the etiological factors have escaped therapeutic control. This is brought about, we believe, by nervous factors that mediate through the autonomic nervous system. Unless the patient has been able to modify his living habits so that nervous strain is at a minimum, any form of therapy will fail. By means of a simple diet, antispasmodics, moderate usage of alkalies or colloidal aluminum hydroxide, and, above all, by the establishment of mental and physical quietude, we can, in the main, obtain results that are satisfactory. In most instances, ambulatory treatment is preferable to complete bed rest in the hospital or home. It is only when these measures fail to produce remissions which are lasting or when complications develop which are not amenable to medical care that surgical intervention is necessary.

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SUCCESSFUL USE OF PRONTOSIL IN A SEVERE CASE OF STREPTOCOCCUS SEPTICEMIA FOLLOWING CYSTOSCOPY AND PERI-URETHRAL ABSCESS

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Several months ago there was introduced into our therapeutic armamentarium a new chemical agent said to be specific for an organism which has always presented a problem to the physician—the Streptococcus. The trade name of this substance—disodium 4-sulphamidophnyl-2-azo-7-acetylamino-1-hydroxynaphthalene 3, 6-disulphonate—is Prontosil. Convincing clinical as well as pharmacologic evidence has thoroughly established its efficacy in Germany and England. In England, its value in infections due to Streptococcus haemolyticus has been particularly stressed and even in cases of well developed blood stream infections, as in puerperal septicemia, recovery has frequently occurred and the mortality rate has been greatly reduced. It has been shown to be effective in the treatment of severe infections due to other forms of Streptococci, and it has been reported to be specific for the Gonococcus.

The following is a striking demonstration of the promptness of action and rapid reduction of temperature following the administration of Prontosil. Perhaps an even more striking result would have been obtained had the dosage been adequate from the beginning.

REPORT OF CASE

The patient was a young man, 20 years of age, who was brought to the Cleveland Clinic Hospital in an ambulance. He was admitted on the general surgical service with the following complaints: chills and fever and abscess at the base of the penis which had been present for two weeks and pain over the left kidney during the preceding four months.

Past history revealed that, at the age of 4 years, he had had scarlet fever and this was followed by mild nephritis. At the age of 15 years a ureteral calculus had been passed. A stormy convalescence followed a cystoscopic examination and ureteral catheterization at this time, and severe cystitis persisted for several months. Possibly several small stones were passed during this period. Following this, the patent's health was good until one year previous to admittance to the hospital when he began to pass cloudy urine and, on analysis, a definite pyuria was found. He was attending school at the time and no further investigation was made. Associated with the pyuria was a chronic aching pain over the left kidney. The pyuria persisted and several severe attacks of pain simulating renal colic occurred.

The patient was taken to the local hospital where an attempt was made to pass a cystoscope but an obstruction was encountered in the membranous urethra. A number 18 Wishard catheter was passed and it was concluded that a urethral stricture was present. The following day he had a severe chill followed by fever of 103° F. The chills continued, as many as two or three occurring each day, and these were followed by a marked elevation in temperature. No further

cystoscopic examinations were made. A roentgenogram of the kidneys, ureters, and bladder showed no evidence of renal lithiasis. The patient was discharged from the hospital after ten days, at which time his temperature was 103° F. During the preceding two months 35 pounds in weight had been lost.

After the patient had been home for two days, he found a soft, painful mass along the urethra at the scrotal junction, extending along the left side of the scrotum. He also experienced some difficulty in passing urine. A physician passed a catheter and the mass was incised. About 60 cc. of creamy pus exuded and a quantity of urine. A drain was placed in the incision and urine continued to drain from the opening. The chills continued to occur and each time the temperature seemed to rise a little higher, reaching 104.8° F. at times.

The patient entered the Cleveland Clinic Hospital on January 31, 1937. The temperature was 101.8° F. and the pulse rate was 108 beats per minute; the blood pressure in millimeters of mercury was 112 systolic, 60 diastolic. His weight was 200 pounds. His appearance was that of a chronically ill but well nourished, sallow male who was perspiring freely and gave evidence of the presence of pain on every movement.

Examination of the head, neck, and chest, aside from those findings described, revealed no abnormalities. The abdomen was flat and soft and no masses or areas of tenderness were palpable. The fist percussion over both costovertebral angles was very painful, especially on the left side and even light palpation on this side produced pain. There was some suggestion of fullness in the left costovertebral angle. An indwelling catheter was in place and some urine also came from an opening just to the left at the base of the penis. It was at this point that the peri-urethral abscess had been opened and there remained an area of redness and induration but there was no purulent drainage. The genitalia were otherwise negative. There were no other positive physical findings.

Diagnoses of urethral fistula, acute cystitis, and acute bilateral pyelonephritis were made. The patient was then transferred to the urological service.

Laboratory findings at this time were: Blood count, red blood cells 4,240,000; hemoglobin 78 per cent; white blood cells 6,100 with 83 per cent neutrophils and 15 per cent lymphocytes; blood urea 51 mg. per hundred cubic centimeters; blood sugar 106 mg. per hundred cubic centimeters, icterus index 10.0. The Wassermann reaction of the blood was negative. A blood culture was taken on entrance and was reported negative for seven consecutive days. The sedimentation rate was elevated to 1.10, and agglutinations for tuluremia and undulant fever were negative. Analysis of the urine showed a specific gravity of 1.017, 2+ albumin, negative for sugar, 5 to 10 red blood cells per high power field and loaded with pus cells, negative for acid-fast bacilli.

Roentgen examination revealed the chest to be normal. A urogram made five days after admission showed prompt function from both kidneys. The right kidney was apparently normal and emptied in one hour while the left showed some dilatation and retention after one hour. The appearance of the calices was somewhat characteristic of that seen in an infectious process.

At cystoscopic examination a number 18 McCarthy cystoscope was passed very easily. The bladder showed evidence of marked cystitis; both ureteral orifices were seen and a catheter was passed to the left kidney. A specimen of urine from this kidney was quite cloudy in appearance. The pH of the urine was 6.5, a few red blood cells were present, 2+ pus, and many organisms, but there were no acid-fast bacilli. A culture of this urine revealed B. coli and B. pyocyaneous.

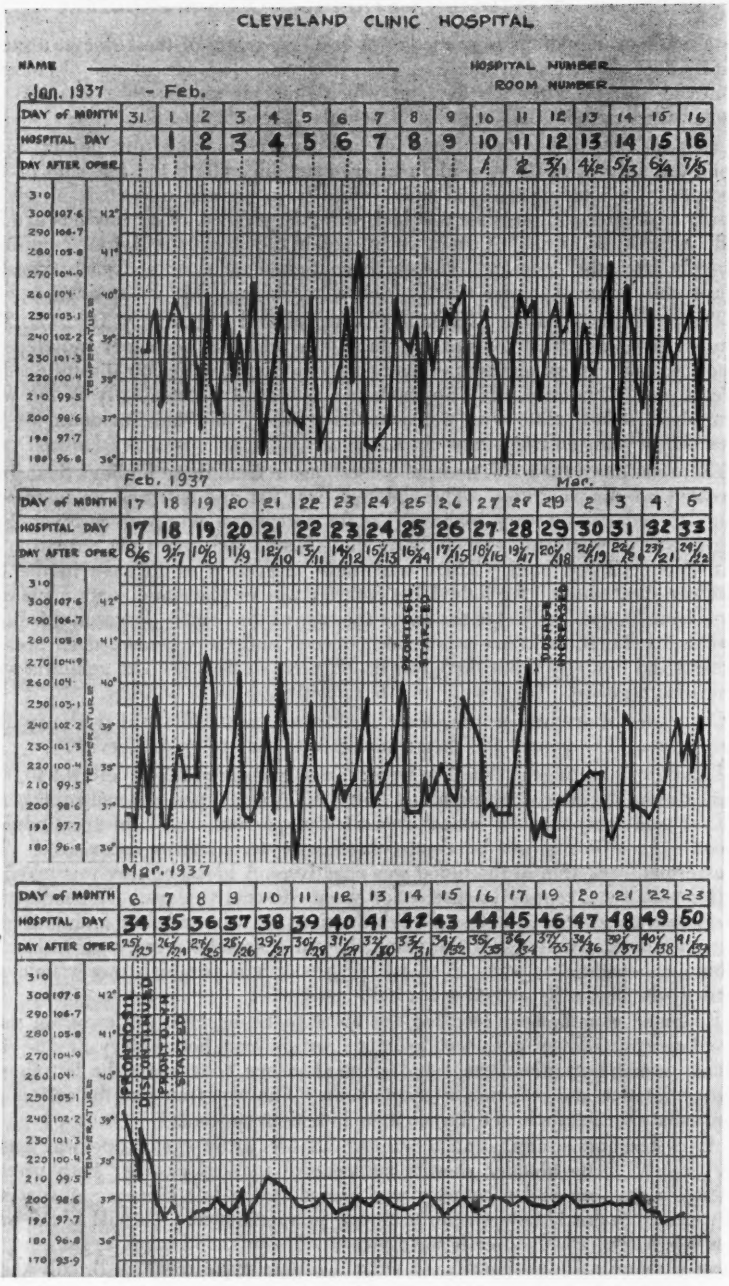

FIGURE 1: Temperature curve from time of admission to time of discharge.

A pyelogram disclosed findings similar to those seen on the urogram and a questionable diagnosis of early tuberculosis of the left kidney was made by the roentgenologist.

During this investigative period which occupied approximately nine days, the patient had one and sometimes two chills each day (Fig. 1). His temperature rose to 104° F. each time with one exception, at which time it reached 105.8° F. The chills seemed to become more severe each day. Between chills, he was quite comfortable, maintained a very good appetite, and his fluid intake and output were very good. Daily analyses of the urine continued to show the same findings as on admission. Repeated cultures of the blood gave negative findings even though the clinical picture was that of septicemia. The white count varied from 8,000 to 15,000 but never became exceedingly high. The value for hemoglobin gradually fell from 78 to 58 per cent and two transfusions, one of 300 cc. and the other of 500 cc. of citrated blood were given during the first week in the hospital.

In view of the clinical and laboratory findings referable to the left kidney, it was explored on the eleventh hospital day in the belief that a perinephritic abscess, carbuncle of the kidney, or possibly multiple abscesses of the kidney might be found. The only abnormality encountered was a marked perinephritis with considerable edema of the fatty tissue about the kidney. The kidney tissue proper appeared grossly quite normal. A No. 16 rubber catheter was sutured into the kidney pelvis, however, in order that the pelvis might be lavaged, thus promoting adequate drainage. The postoperative convalescence was uneventful and the general condition continued as it was before the surgical intervention. Four days after operation, another transfusion of 800 cc. of citrated blood was given. All types of urinary antiseptics, including mendelic acid therapy, gave no results.

On the sixteenth hospital day, another blood culture was taken and on the twenty-fourth hospital day it was reported positive for Streptococcus, nonhemolytic. Another transfusion of 800 cc. citrated blood was given.

At this time the new therapeutic agent, Prontosil, was introduced and 5 cc. of the substance was given every four hours by deep intramuscular injection in the gluteal muscles. Some response followed and for thirty-six hours the patient had no chills. This medication was continued for 4 days until a total of 120 cc. of Prontosil had been given. The temperature then began to rise again and another chill ensued. It was realized that the dosage had been inadequate so it was increased to 20 cc. every four hours, being given in the same manner. This was continued for five days until the total amount of Prontosil given had reached 720 cc. Definite response then began to be evident; only one chill had occurred during this time, and, on the thirty-fifth hospital day the temperature was normal. Prontolyn was then given by mouth, gr. 5, three times daily until the patient left the hospital and the temperature continued to remain normal. Repeated blood cultures gave negative findings.

The general condition immediately began to improve following the increase in the dosage of Prontosil and the urethral fistula closed entirely. During the hospital stay, 70 pounds in weight were lost. On the forty-fourth hospital day, the patient was up, walking about his room, and on the fiftieth day he was discharged from the hospital. Four weeks after discharge, word was received from the patient's mother stating he had been feeling fine, had gained 25 pounds in weight, and was normal in every respect.

Discussion

Considering the severity of the infection in this case and the general condition of the patient, it is difficult to resist the conclusion that the remarkable improvement was due chiefly to the introduction of treatment with Prontosil. After having almost despaired of saving this young man, as it was quite evident that he was in the terminal stages of a fatal infection, his prompt recovery was astonishing.

No severe toxic effects followed administration of the drug even though it was given in very large doses. Irritation of the urinary tract existed to a mild degree before this treatment was instituted but it was slightly more severe following the fifth day of Prontosil therapy. A few red blood cells were found in the urine and there were numerous epithelial cells. These disappeared following cessation of treatment with Prontosil.

The value for hemoglobin diminished slightly when Prontosil therapy was begun and it continued to be below normal even at the time of discharge. No definite determination was made to establish the presence of sulphemoglobinemia. Several such cases have been reported following the use of Prontosil. Such a finding is most likely to occur, however, when some form of magnesium sulphate is administered during the period when Prontosil is given.

Prontosil and Prontolyn have been employed at the Cleveland Clinic in the treatment of septic sore throat, suppurative otitis media, streptococcic infections of the hand, brain abscess, and several cases of Streptococcus septicemia. In all cases there has been a striking reduction of temperature and general improvement of the patient. Its use in the treatment of gonorrhea has been encouraging but not definitely verified at this time.

A tremendous interest has been manifested in Prontosil and Prontolyn and they are worthy of consideration by every physician who is treating infections due to the Streptococcus.